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BOX PROVISIONAL APPLICATION
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WASHINGTON, DC 20231

Express Mail No.: EV 124826408 US
Attorney Docket No.: 2003080-0117 (SK-1071-PROV)
Date Filed: March 28, 2003

PROVISIONAL APPLICATION TRANSMITTAL

(REQUEST FOR FILING A PROVISIONAL APPLICATION FOR PATENT UNDER 37 CFR § 1.53(C))

Dear Sir:

Please find enclosed a provisional patent application and papers as follows for:

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Title of the Invention: MIGRASTATIN ANALOGS AND USES THEREOF

A) ENCLOSED APPLICATION PARTS:

1)	X	**Specification**	PAGES	131
	X	**Claims**	PAGES	19
	X	**Abstract**	PAGES	1
	X	**Figures**	PAGES	1
			TOTAL:	152

B) OTHER ACCOMPANYING APPLICATION PARTS:

3) X Return Receipt Postcard (MPEP § 503) (specifically itemized)

4) ___ Application Data Sheet. See 37 CFR § 1.76

5) X **OTHER:** (if applicable, specified below)

X **Appendix A** PAGES 11

C) CORRESPONDENCE ADDRESS:

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D) METHOD OF PAYMENT OF FILING FEES:

X Applicant claims small entity status. See 37 CFR §1.27.

___ Statement Verifying Small Entity Status (optional)

X A check or money order is enclosed to cover the filing fees.

X The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-1721.

FILING FEE AMOUNT ($): $ 80.00

THE INVENTION WAS MADE, IN PART, BY AN AGENCY OF THE UNITED STATES GOVERNMENT OR UNDER A CONTRACT WITH AN AGENCY OF THE UNITED STATES GOVERNMENT:

_____NO.

__X__YES, THE NAME OF THE U.S. GOVERNMENT AGENCY AND THE GOVERNMENT CONTRACT NUMBER ARE : **(1) GRANT 08748 – NATIONAL CANCER INSTITUTE; AND (2) GRANT AI-16943-NATIONAL INSTITUTES OF HEALTH.**

Respectfully Submitted,

Dated: March 28, 2003

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner For Patents, Washington, D.C. 20231
Kathy Hart Gagnon

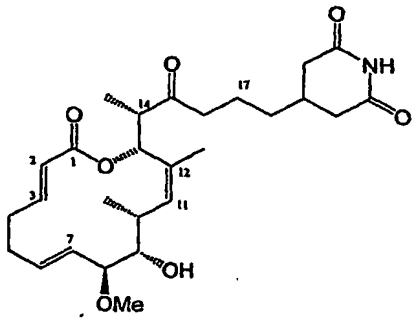
MIGRASTATIN ANALOGS AND USES THEREOF

GOVERNMENT SUPPORT

[0001] The invention was supported in part by Grant No.: 08748 from the National Cancer Institute, Grant AI-16943 from the National Institutes of Health and by Postdoctoral Fellowships for Christoph Gaul (Deutscher Akademischer Austauschdienst, DAAD) and Jon Tryggvi Njardarson (General Motors Cancer Research Program). The U.S. government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

[0002] Migrastatin (1) is a novel 14-membered ring macrolide natural product, that was first isolated from a cultured broth of *Steptomyces* sp. MK929-43F1 by Imoto *et al.* (see, Nakae *et al.*, *J. Antibiot.*, **2000**, *53*, 1130-1136; and Nakae *et al.*, *J. Antibiot.*, **2000**, *53*, 1228-1230). It was recently reported that cultures of *Steptomyces platensis* also produce Migrastatin (see, Woo *et al.*, *J. Antibiot.*, **2002**, *55*, 141-146).



(1)

[0003] Migrastatin has been shown to inhibit both migration and anchorage-independent growth of human tumor cells (see, Nakae *et al.*, *J. Antibiot.*, **2001**, *54*, 1104-1107), and has sparked interest in the area of cancer research. Specifically, migration of tumor cells is part of the complex process of metastasis, which is the leading cause of death in cancer patients. Therefore, Migrastatin and derivatives thereof hold great potential as therapeutic agents for the treatment of cancer.

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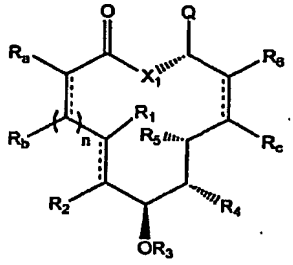
[0004] After initial isolation and reporting of this compound, several groups explored the possibility of preparing derivatives and/or further exploring their biological activity. Each of these groups, however, was only able to obtain Migrastatin and derivatives thereof by fermentation techniques and/or by modifications to the natural product, and thus was limited in the number and types of derivatives that could be prepared and/or evaluated for biological activity.

[0005] Clearly, there remains a need to develop synthetic methodologies to access and examine the therapeutic effect of a variety of novel analogues of Migrastatin, particularly those that are inaccessible by making modifications to the natural product. It would also be of particular interest to develop novel compounds that exhibit a favorable therapeutic profile *in vivo* (*e.g.*, are safe and effective).

SUMMARY OF THE INVENTION

[0006] As discussed above, there remains a need for the development of novel Migrastatin analogs and the evaluation of their biological activity. The present invention provides novel compounds of general formula (I),



(I)

and pharmaceutical compositions thereof, as described generally and in subclasses herein, which compounds are useful as inhibitors of cell migration, exhibit antiangiogenic activity, and/or have an anti-proliferative effect. Thus these compounds are useful, for example, for the treatment of various disorders including disorders involving malignancy or increased angiogenesis.

[0007] In another aspect, the present invention provides methods for identifying derivatives useful in the preparation of pharmaceutical compositions for the treatment of cancer. In yet another aspect, the present invention provides methods for decreasing migration of tumor cells.

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In a further aspect, the present invention provides methods for decreasing anchorage-independent growth of tumor cells. In yet another aspect, the present invention provides methods for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of the compound of the invention in an amount effective to inhibit angiogenesis.

DEFINITIONS

[0008] The term "aliphatic", as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched) or branched aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl moieties. Thus, as used herein, the term "alkyl" includes straight and branched alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl" and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl" and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms.

[0009] In certain embodiments, the alkyl, alkenyl and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, n-hexyl, sec-hexyl, moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

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[0010] The term "alicyclic", as used herein, refers to compounds which combine the properties of aliphatic and cyclic compounds and include but are not limited to cyclic, or polycyclic aliphatic hydrocarbons and bridged cycloalkyl compounds, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "alicyclic" is intended herein to include, but is not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, which are optionally substituted with one or more functional groups. Illustrative alicyclic groups thus include, but are not limited to, for example, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, $-CH_2$-cyclobutyl, cyclopentyl, $-CH_2$-cyclopentyl-n, cyclohexyl, $-CH_2$-cyclohexyl, cyclohexenylethyl, cyclohexanylethyl, norborbyl moieties and the like, which again, may bear one or more substituents.

[0011] The term "alkoxy" (or "alkyloxy"), or "thioalkyl" as used herein refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom or through a sulfur atom. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4 aliphatic carbon atoms. Examples of alkoxy, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy and n-hexoxy. Examples of thioalkyl include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, and the like.

[0012] The term "alkylamino" refers to a group having the structure -NHR'wherein R' is alkyl, as defined herein. The term "aminoalkyl" refers to a group having the structure NH_2R'-, wherein R' is alkyl, as defined herein. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4 aliphatic carbon atoms. Examples of alkylamino include, but are not limited to, methylamino, ethylamino, iso-propylamino and the like.

[0013] Some examples of substituents of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0014] In general, the terms "aryl" and "heteroaryl", as used herein, refer to stable mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. It will also be appreciated that aryl and heteroaryl moieties, as defined herein may be attached via an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, alkyl or heteroalkyl moiety and thus also include –(aliphatic)aryl, -(heteroaliphatic)aryl, -(aliphatic)heteroaryl, -(heteroaliphatic)heteroaryl, –(alkyl)aryl, -(heteroalkyl)aryl, -(heteroalkyl)aryl, and –(heteroalkyl)heteroaryl moieties. Thus, as used herein, the phrases "aryl or heteroaryl" and "aryl, heteroaryl, –(aliphatic)aryl, -(heteroaliphatic)aryl, -(aliphatic)heteroaryl, -(heteroaliphatic)heteroaryl, –(alkyl)aryl, -(heteroalkyl)aryl, -(heteroalkyl)aryl, and –(heteroalkyl)heteroaryl" are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substitutents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In certain embodiments of the present invention, "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. In certain embodiments of the present invention, the term "heteroaryl", as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O

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and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

[0015] It will be appreciated that aryl and heteroaryl groups (including bicyclic aryl groups) can be unsubstituted or substituted, wherein substitution includes replacement of one, two or three of the hydrogen atoms thereon independently with any one or more of the following moieties including, but not limited to: aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0016] The term "cycloalkyl", as used herein, refers specifically to groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of aliphatic, heteroaliphatic or heterocyclic moieties, may optionally be substituted with substituents including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl,

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or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0017] The term "heteroaliphatic", as used herein, refers to aliphatic moieties in which one or more carbon atoms in the main chain have been substituted with a heteroatom. Thus, a heteroaliphatic group refers to an aliphatic chain which contains one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched or linear unbranched. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, but not limited to aliphatic; alicyclic; heteroaliphatic; heteroalicyclic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0018] The term "heteroalicyclic", as used herein, refers to compounds which combine the properties of heteroaliphatic and cyclic compounds and include but are not limited to saturated and unsaturated mono- or polycyclic heterocycles such as morpholino, pyrrolidinyl, furanyl, thiofuranyl, pyrrolyl etc., which are optionally substituted with one or more functional groups, as defined herein.

[0019] Additionally, it will be appreciated that any of the alicyclic or heteroalicyclic moieties described above and herein may comprise an aryl or heteroaryl moiety fused thereto. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0020] The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0021] The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0022] The term "heterocycloalkyl" or "heterocycle", as used herein, refers to a non-aromatic 5-, 6- or 7- membered ring or a polycyclic group, including, but not limited to a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl. In certain embodiments, a "substituted heterocycloalkyl or heterocycle" group is utilized and as used herein, refers to a heterocycloalkyl or heterocycle group, as defined above, substituted by the independent replacement of one, two or three of the hydrogen atoms thereon with but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any

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of the aryl or heteroaryl substitutents described above and herein may be substituted or unsubstituted. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples, which are described herein.

[0023] As used herein, the terms "aliphatic", "heteroaliphatic", "alkyl", "alkenyl", "alkynyl", "heteroalkyl", "heteroalkenyl", "heteroalkynyl", and the like encompass substituted and unsubstituted, saturated and unsaturated, and linear and branched groups. Similarly, the terms "alicyclic", "heteroalicyclic", "heterocycloalkyl", "heterocycle" and the like encompass substituted and unsubstituted, and saturated and unsaturated groups. Additionally, the terms "cycloalkyl", "cycloalkenyl", "cycloalkynyl", "heterocycloalkyl", "heterocycloalkenyl", "heterocycloalkynyl", "aryl", "heteroaryl" and the like encompass both substituted and unsubstituted groups.

[0024] The phrase, "pharmaceutically acceptable derivative", as used herein, denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of such compound, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include among others pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety, which is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species. An example of a pro-drug is an ester, which is cleaved *in vivo* to yield a compound of interest. Pro-drugs of a variety of compounds, and materials and methods for derivatizing the parent compounds to create the pro-drugs, are known and may be adapted to the present invention. Certain exemplary pharmaceutical compositions and pharmaceutically acceptable derivatives will be discussed in more detail herein below.

[0025] By the term "protecting group", has used herein, it is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In preferred embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected reactions; the protecting group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the other functional groups; the protecting group forms an easily separable derivative (more preferably without the generation of

new stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. As detailed herein, oxygen, sulfur, nitrogen and carbon protecting groups may be utilized. For example, in certain embodiments, as detailed herein, certain exemplary oxygen protecting groups are utilized. These oxygen protecting groups include, but are not limited to methyl ethers, substituted methyl ethers (*e.g.*, MOM (methoxymethyl ether), MTM (methylthiomethyl ether), BOM (benzyloxymethyl ether), PMBM or MPM (p-methoxybenzyloxymethyl ether), to name a few), substituted ethyl ethers; substituted benzyl ethers, silyl ethers (*e.g.*, TMS (trimethylsilyl ether), TES (triethylsilylether), TIPS (triisopropylsilyl ether), TBDMS (t-butyldimethylsilyl ether), tribenzyl silyl ether, TBDPS (t-butyldiphenyl silyl ether), to name a few), esters (*e.g.*, formate, acetate, benzoate (Bz), trifluoroacetate, dichloroacetate, to name a few), carbonates, cyclic acetals and ketals. In certain other exemplary embodiments, nitrogen protecting groups are utilized. These nitrogen protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (*e.g.*, Troc), to name a few) amides, cyclic imide derivatives, N-Alkyl and N-Aryl amines, imine derivatives, and enamine derivatives, to name a few. Certain other exemplary protecting groups are detailed herein, however, it will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the present invention. Additionally, a variety of protecting groups are described in "Protective Groups in Organic Synthesis" Third Ed. Greene, T.W. and Wuts, P.G., Eds., John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

Brief Description of the Drawing

[0026] Figure 1A depicts a ^{1}H NMR spectrum of synthetic Migrastatin.

[0027] Figure 1B depicts a ^{1}H NMR spectrum of naturally occurring Migrastatin.

Description of Certain Preferred Embodiments of the Invention

[0028] In recognition of the need to access and further explore the biological activity of novel Migrastatin analogs, and this class of macrocycles in general, the present invention

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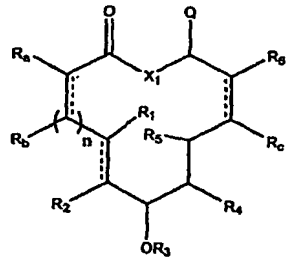
provides novel macrocyclic compounds, as described in more detail herein, which exhibit the ability to inhibit cell migration. Therefore, the compounds hold promise as angiogenesis inhibitors. Thus, the compounds of the invention, and pharmaceutical compositions thereof, are useful as antiangiogenesis agents for the treatment of cancer and/or abnormal cell proliferation. In certain embodiments, the compounds of the present invention can be used for the treatment of diseases and disorders including, but not limited to solid tumor cancers, metastasis, ocular angiogenic diseases, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasias, rubeosis, solid tumors, blood born tumors, leukemias, tumor metastases, benign tumors, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas, rheumatoid arthritis, psoriasis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, or wound granulation, to name a few.

[0029] 1) General Description of Compounds of the Invention

[0030] In certain embodiments, the compounds of the invention include compounds of the general formula (I) as further defined below:



(I)

wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

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R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

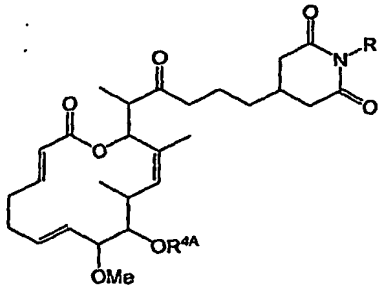
n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or a nitrogen protecting group;

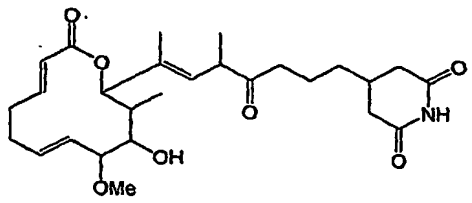
Q is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{Q1}$, -NO_2, -COR^{Q1}, -CO_2R^{Q1}, -$NR^{Q1}C(=O)R^{Q2}$, -$NR^{Q1}C(=O)OR^{Q2}$, -$CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{Q1}; wherein W is independently -O-, -S- or -NR^{Q3}-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

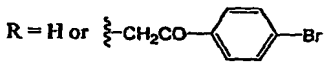
pharmaceutically acceptable derivatives thereof.

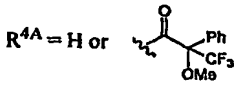
[0031] In certain embodiments of compounds described directly above and compounds as described in certain classes and subclasses herein, inventive compounds do not have the following structure:



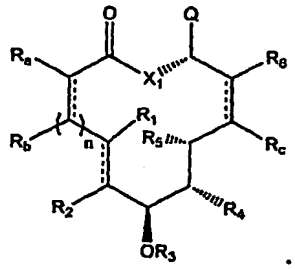
or







[0032] In certain other embodiments, compounds of formula (I) have the following stereochemistry:



[0033] In certain other embodiments, compounds of formula (I) are defined as follows:

R_1 and R_2 are each independently hydrogen or substituted or unsubstituted lower alkyl;

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R_3 is hydrogen, or substituted or unsubstituted lower alkyl or aryl; a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, or substituted or unsubstituted lower alkyl; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 and R_6 are each independently hydrogen or substituted or unsubstituted lower alkyl;

R_a and each occurrence of R_b are independently hydrogen, halogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}-$, wherein each occurrence of R^{a1}, and R^{a3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an epoxide or a substituted or unsubstituted cyclopropyl moiety;

R_c is hydrogen, halogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}-$, wherein each occurrence of R^{c1} and R^{c3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an epoxide or a substituted or unsubstituted cyclopropyl moiety;

n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}-$, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

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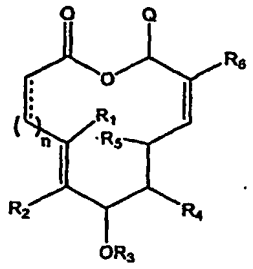
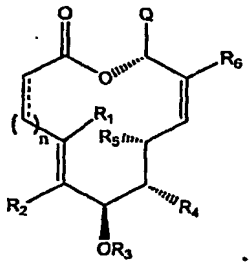
[0034] In certain embodiments, the present invention defines certain classes of compounds which are of special interest. For example, one class of compounds of special interest includes those compounds having the structure of formula (I) in which R_a, R_b and R_c are each hydrogen, X is O and the compound has the structure:

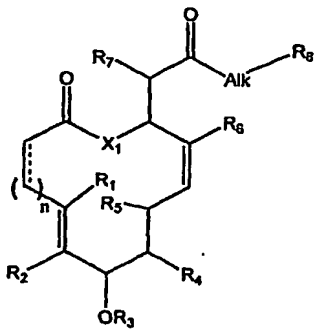


wherein R_1-R_6, n and Q are as defined in classes and subclasses herein.

[0035] In certain exemplary embodiments, compounds of the invention shown directly above have the following stereochemistry:



[0036] Another class of compounds of special interest includes compounds having the structure of formula (I) in which R_a, R_b and R_c are each hydrogen, X_1 is O, Q is a carbonyl-containing moiety and the compound has the structure:



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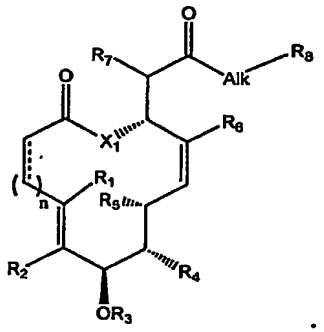
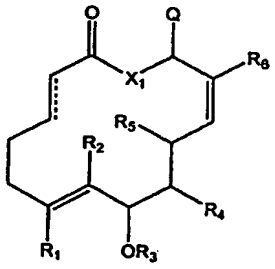
wherein R_1-R_6, n and X are as defined in clases and subclasses herein; R_7 is a substituted or unsubstituted lower alkyl or heteroalkyl moiety, and R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; and R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety.

[0037] In certain exemplary embodiments, compounds of the invention shown directly above have the following stereochemistry:



[0038] Another class of compounds of special interest includes compounds having the structure of formula (I) in which R_a, R_b and R_c are each hydrogen, n is 3 and the compound has the structure:



wherein R_1-R_6, Q and X are as defined in classes and subclasses herein.

[0039] In certain exemplary embodiments, compounds of the invention shown directly above have the following stereochemistry:

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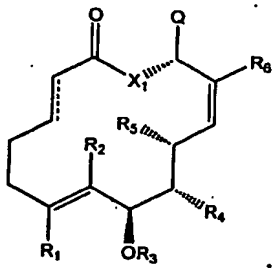
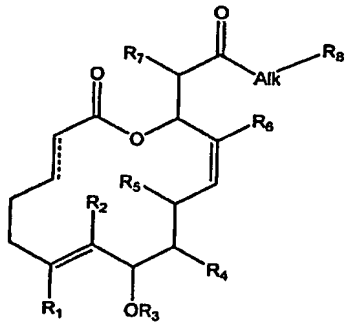
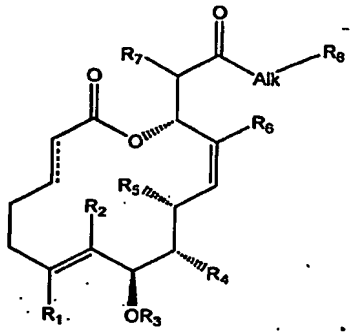


[0040] Another class of compounds of special interest includes compounds having the structure of formula (I) in which R_a, R_b and R_c are each hydrogen, X is O, n is 3, Q is a carbonyl-containing moiety, and the compound has the structure:

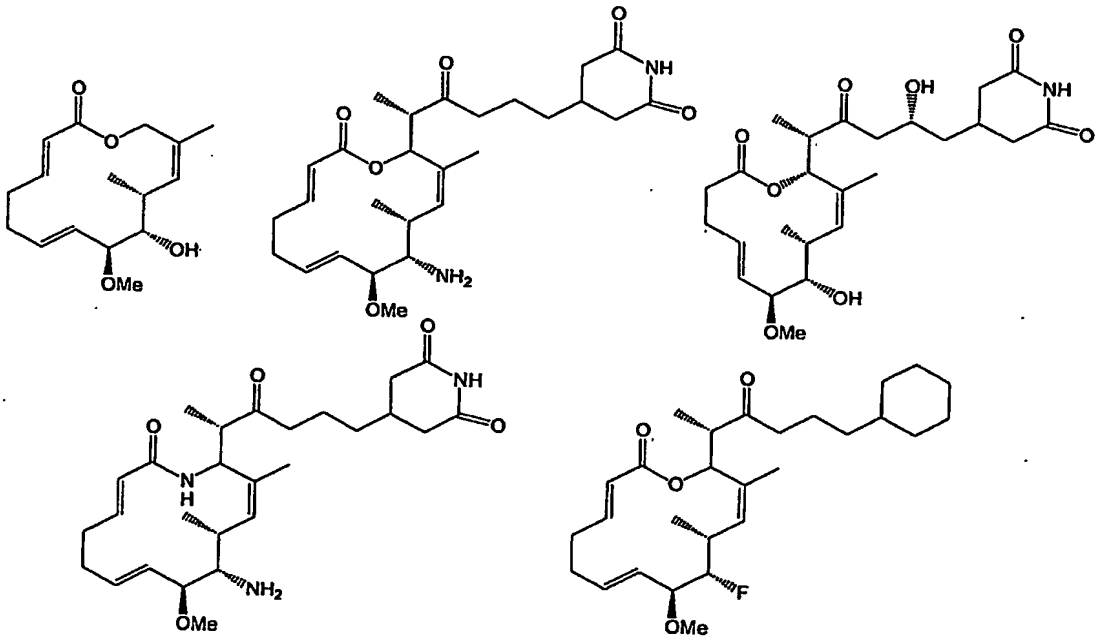


wherein R_1-R_6 are as previously defined; R_7 is a substituted or unsubstituted lower alkyl or heteroalkyl moiety; R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl.

[0041] In certain exemplary embodiments, compounds of the invention shown directly above have the following stereochemistry:



[0042] The following structures illustrate several exemplary types of compounds of these classes. Additional compounds are described in the Exemplification herein. Other compounds of the invention will be readily apparent to the reader:



[0043] A number of important subclasses of each of the foregoing classes deserve separate mention; these subclasses include subclasses of the foregoing classes in which:

[0044] i) R_1 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or -

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NR^{1C}-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0045] ii) R_1 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0046] iii) R_1 is hydrogen or lower alkyl;

[0047] iv) R_1 is hydrogen;

[0048] v) R_2 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0049] vi) R_2 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0050] vii) R_2 is hydrogen or lower alkyl;

[0051] viii) R_2 is hydrogen;

[0052] ix) R_1 and R_2 are each hydrogen;

[0053] x) R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0054] xi) R_1 and R_2, taken together, form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0055] xii) R_1 and R_2, taken together, form an epoxide;

[0056] xiii) R_1 and R_2, taken together, form a substituted or unsubstituted cyclopropyl;

[0057] xiv) R_3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, silyl, $-C(=O)R^x$, $-C(=S)R^x$, $-C(=NR^x)R^y$, $-SO_2R^x$, wherein R^x and R^y are each

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independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, $-C(=O)R^A$ or $-ZR^A$, wherein Z is –O-, -S-, $-NR^B$, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety;

[0058] xv) R_3 is hydrogen, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

[0059] xvi) R_3 is hydrogen, lower alkyl, aryl, a prodrug moiety or an oxygen protecting group;

[0060] xvii) R_3 is hydrogen, lower alkyl, aryl or an oxygen protecting group;

[0061] xviii) R_3 is methyl;

[0062] xix) the carbon atom bearing R_4 is of *R*-configuration;

[0063] xx) the carbon atom bearing R_4 is of *S*-configuration

[0064] xxi) R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, or substituted or unsubstituted lower alkyl; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

[0065] xxii) R_4 is a halogen selected from fluorine, chlorine, bromine, and iodine;

[0066] xxiii) R_4 is fluorine;

[0067] xxiv) the carbon atom bearing R_4 is of *R*-configuration, and R_4 is a halogen selected from fluorine, chlorine, bromine, and iodine;

[0068] xxv) the carbon atom bearing R_4 is of *R*-configuration, and R_4 is fluorine;

[0069] xxvi) R_4 is OR^{4A}, wherein R^{4A} is hydrogen, a substituted or unsubstituted lower alkyl; a prodrug moiety or an oxygen protecting group;

[0070] xxvii) R_4 is OH;

[0071] xxviii) R_4 is $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, a substituted or unsubstituted lower alkyl; a prodrug moiety or a nitrogen protecting group; or R^{4A}

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and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

[0072] xxix) R_4 is $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, alkyl, alkenyl, $-C(=O)R^x$, $-C(=O)OR^x$, $-SR^x$, SO_2R^x, or R^{4A} and R^{4B}, taken together form a moiety having the structure $=CR^xR^y$, wherein R^{4A} and R^{4B} are not simultaneously hydrogen and R^x and R^y are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl, heteroaryl, $-C(=O)R^A$ or $-ZR^A$, wherein Z is –O-, -S-, $-NR^B$, wherein each occurrence of R^A and R^B is independently hydrogen, or an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety;

[0073] xxx) R_4 is NH_2;

[0074] xxxi) R_5 is hydrogen or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0075] xxxii) R_5 is hydrogen or substituted or unsubstituted lower alkyl;

[0076] xxxiii) R_5 is methyl;

[0077] xxxiv) R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0078] xxxv) R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0079] xxxvi) R_6 is is hydrogen or substituted or unsubstituted lower alkyl;

[0080] xxxvii) R_6 is methyl;

[0081] xxxviii) R_5 and R_6 are each methyl;

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[0082] xxxix) R_a is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0083] xl) R_a is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0084] xli) R_a is hydrogen or lower alkyl;

[0085] xlii) R_a is hydrogen;

[0086] xliii) R_b is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0087] xliv) R_b is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0088] xlv) R_b is hydrogen or lower alkyl;

[0089] xlvi) R_b is hydrogen;

[0090] xlvii) R_a and R_b are each hydrogen;

[0091] xlviii) R_a and R_b, taken together, form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0092] xlix) R_a and R_b, taken together, form an epoxide;

[0093] l) R_a and R_b, taken together, form a substituted or unsubstituted cyclopropyl;

[0094] li) R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

[0095] lii) R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{1C}-$, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0096] liii) R_c is hydrogen or lower alkyl;

[0097] liv) R_c is hydrogen;

[0098] lv) R_c and R_6, taken together, form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety;

[0099] lvi) R_c and R_6, taken together, form an epoxide;

[0100] lvii) R_c and R_6, taken together, form a substituted or unsubstituted cyclopropyl;

[0101] lviii) X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, or a nitrogen protecting group;

[0102] lix) X_1 is O or NR^{X1}; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, or a nitrogen protecting group;

[0103] lx) X_1 is O;

[0104] lxi) X_1 is NH;

[0105] lxii) n is an integer from 1 to 5;

[0106] lxiii) n is 3;

[0107] lxiv) Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; or $-WR^{Q1}$; wherein W is

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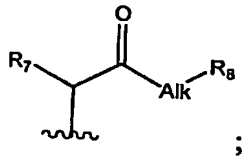
independently -O-, -S- or -NR^{Q3}-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety

[0108] lxv) Q is a substituted or unsubstituted carbonyl-containing alkyl or heteroalkyl moiety;

[0109] lxvi) Q comprises a carbonyl linked to a carbocyclic, heterocyclic, aryl or heteroaryl moiety through a C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl;

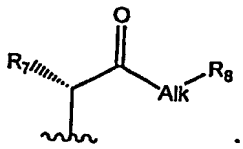
[0110] lxvii) Q has the structure:



;

wherein R_7 is a substituted or unsubstituted lower alkyl or heteroalkyl moiety; R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl;;

[0111] lxviii) Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl

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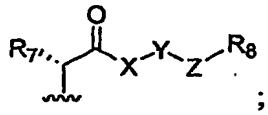
moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl;

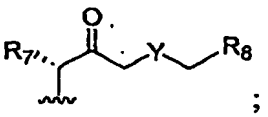
[0112] lxix) Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}-$, $-CHOR^{Z1}$, $-CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety;

[0113] lxx) Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and Y is a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}-$, $-CHOR^{Z1}$, $-CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO,

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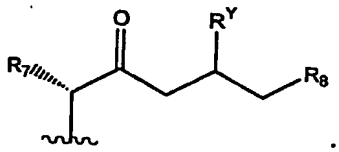
$CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety;

[0114] lxxi) Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety;

[0115] lxxii) R_7 is substituted or unsubstituted lower alkyl;

[0116] lxxiii) R_7 is methyl;

[0117] lxxiv) R^Y is hydrogen;

[0118] lxxv) R^Y is a halogen selected from fluorine, chlorine, bromine, and iodine;

[0119] lxxvi) R^Y is fluorine;

[0120] lxxvii) R^Y is OR^{Y1}, wherein R^{Y1} is hydrogen, a substituted or unsubstituted lower alkyl; a prodrug moiety or an oxygen protecting group;

[0121] lxxviii) R^Y is OH;

[0122] lxxix) R^Y is $NR^{Y1}R^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, a substituted or unsubstituted lower alkyl; a prodrug moiety or a nitrogen protecting group; or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

[0123] lxxx) R^Y is NH_2;

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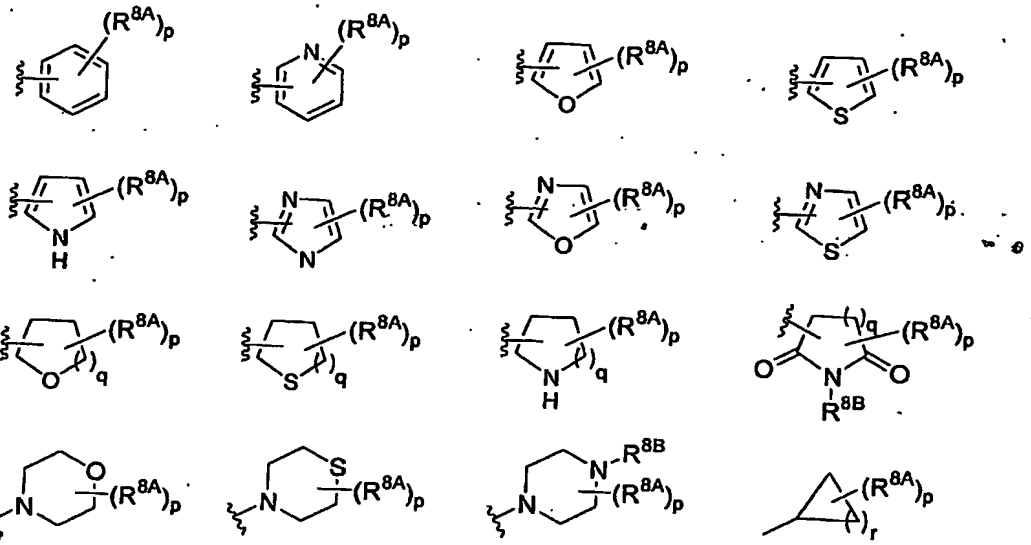
[0124] lxxxi) R_8 is one of:



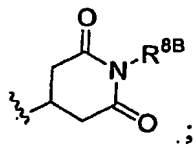
;

wherein p is an integer from 0 to 5; q is 1 or 2, r is an integer from 1 to 6; each occurrence of R^{8A} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{8C}$, $-SR^{8C}$, $-N(R^{8C})_2$, $-SO_2N(R^{8C})_2$, $-(C=O)N(R^{8C})_2$, halogen, -CN, $-NO_2$, $-(C=O)OR^{8C}$, $-N(R^{8C})(C=O)R^{8D}$, wherein each occcurrence of R^{8C} and R^{8D} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; and each occurrence of R^{8B} is independently hydrogen or lower alkyl;

[0125] lxxxii) R_8 is substituted or unsubstituted cycloalkyl;

[0126] lxxxiii) R_8 is substituted or unsubstituted cyclohexyl;

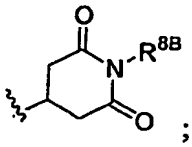
[0127] lxxxiv) R_8 has the structure:



;

wherein R^{8B} is hydrogen or lower alkyl;

[0128] lxxxv) R_8 has the structure:



;

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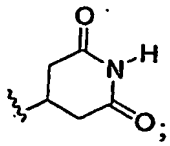
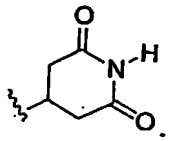
wherein R^{8B} is hydrogen or methyl;

[0129] lxxxvi) R_8 has the structure:



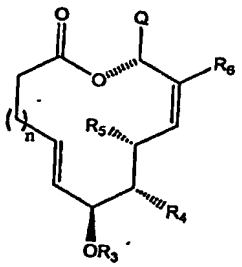
; and/or

[0130] lxxxvii) X_1 is O or NH; and R_8 has the structure:



[0131] As the reader will appreciate, compounds of particular interest include, among others, those which share the attributes of one or more of the foregoing subclasses. Some of those subclasses are illustrated by the following sorts of compounds:

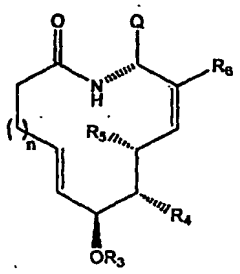
[0132] *I) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*



wherein R_3-R_6, n and Q are as defined in classes and subclasses herein. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen

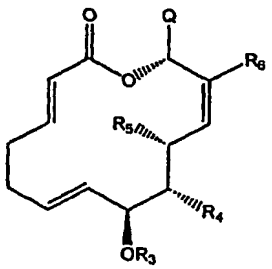
selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2.

[0133] ***II) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein R_3-R_6, n and Q are as defined in classes and subclasses herein. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2.

[0134] ***III) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



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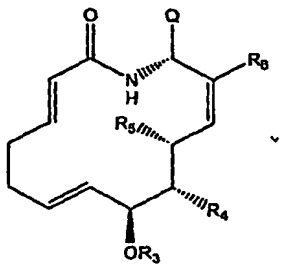
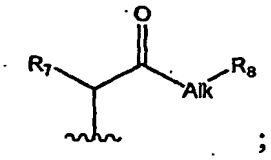
wherein R_3-R_6 and Q are as defined in classes and subclasses herein. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2.

[0135] *IV) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*



wherein R_3-R_6 and Q are as defined in classes and subclasses herein. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2.

[0136] In certain other embodiments, for compounds of classes I)-IV) above, Q is a substituted or unsubstituted carbonyl-containing alkyl or heteroalkyl moiety. In certain exemplary embodiments, Q comprises a carbonyl linked to a carbocyclic, heterocyclic, aryl or heteroaryl moiety through a C_{0-6}alkylidene or C_{0-6}alkenylidene moiety. In certain embodiments, Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; and R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety. In certain embodiments, R_7 is lower alkyl. In certain other embodiments, Alk is a C_3 alkylidene moiety. In yet other embodiments, R_8 is one of:

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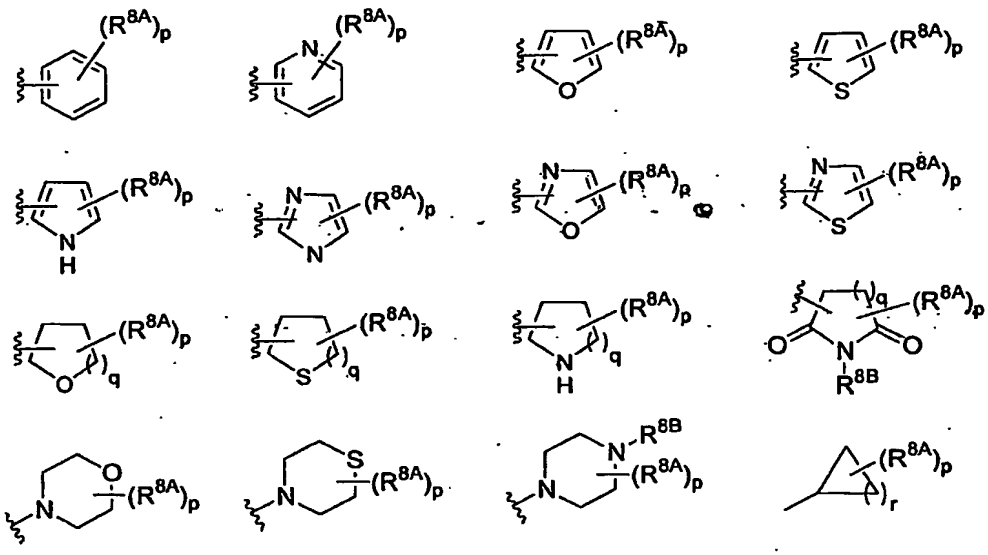
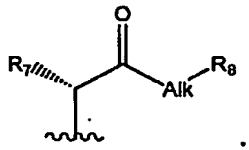


wherein p is an integer from 0 to 5; q is 1 or 2, r is an integer from 1 to 6; each occurrence of R^{8A} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{8C}$, $-SR^{8C}$, $-N(R^{8C})_2$, $-SO_2N(R^{8C})_2$, $-(C=O)N(R^{8C})_2$, halogen, -CN, $-NO_2$, $-(C=O)OR^{8C}$, $-N(R^{8C})(C=O)R^{8D}$, wherein each occcurrence of R^{8C} and R^{8D} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; and each occurrence of R^{8B} is independently hydrogen or lower alkyl.

[0137] In certain exemplary embodiments, Q has the following stereochemistry:



[0138] ***V) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***

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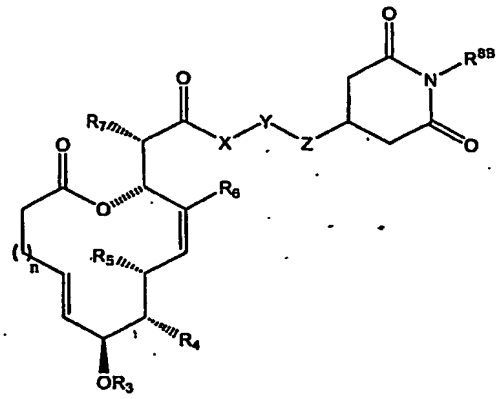
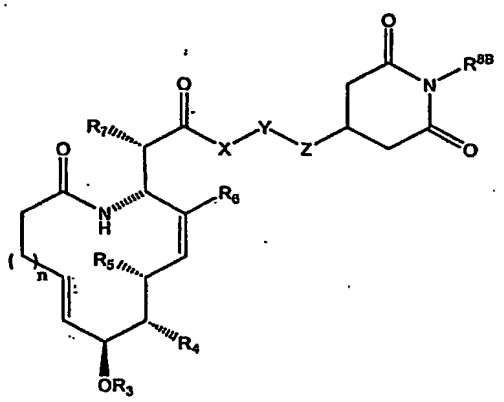


wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, -NR^{Z1}-, –$CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, C=N(R^{Y1}) or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is

methyl. In certain other embodiments, X and Z are each CH_2 and Y is –CHOH, -$CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0139] *VI) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*



wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, -NR^{Z1}-, –$CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, C=N(R^{Y1}) or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or

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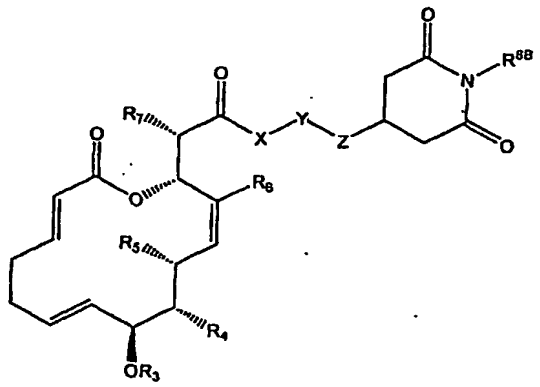
unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, X and Z are each CH_2 and Y is –CHOH, -$CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0140] ***VII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, -NR^{Z1}-, –$CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, C=N(R^{Y1}) or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain

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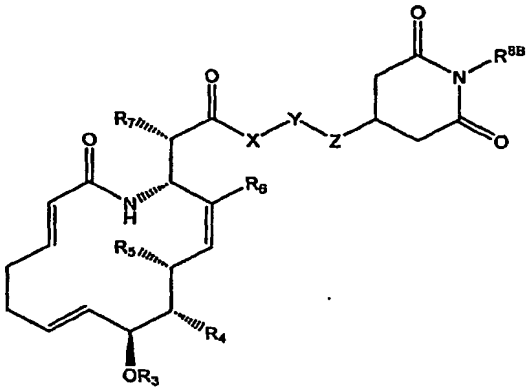
embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, X and Z are each CH_2 and Y is –CHOH, -$CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0141] ***VIII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}$-, $–CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.. In certain embodiments, R_3 is

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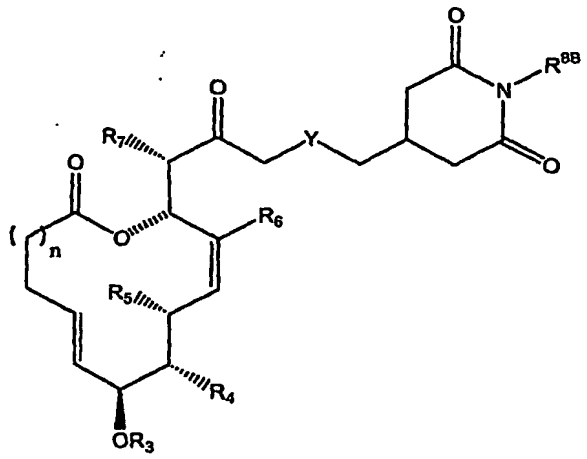
hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, X and Z are each CH_2 and Y is –CHOH, -$CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0142] In certain embodiments, for compounds of classes V-VIII above, –X-Y-Z together represents the moiety –CH_2-Y-CH_2-; wherein Y is –$CHOR^{Y1}$, -$CHNR^{Y1}R^{Y2}$, C=O, C=S, C=N(R^{Y1}) or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety.

[0143] ***IX) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



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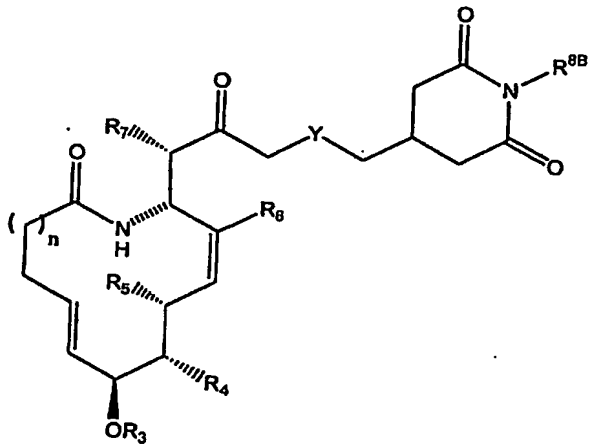
wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and Y is $-CHOR^{Y1}$, $-CHNR^{Y1}R^{Y2}$, C=O, C=S, $C=N(R^{Y1})$ or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, Y is –CHOH, $-CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0144] ***X) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



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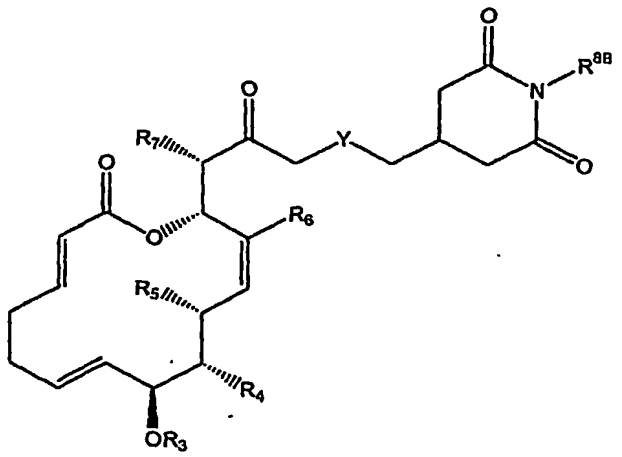
wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and Y is $-CHOR^{Y1}$, $-CHNR^{Y1}R^{Y2}$, C=O, C=S, $C=N(R^{Y1})$ or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, Y is –CHOH, $-CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0145] ***XI) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



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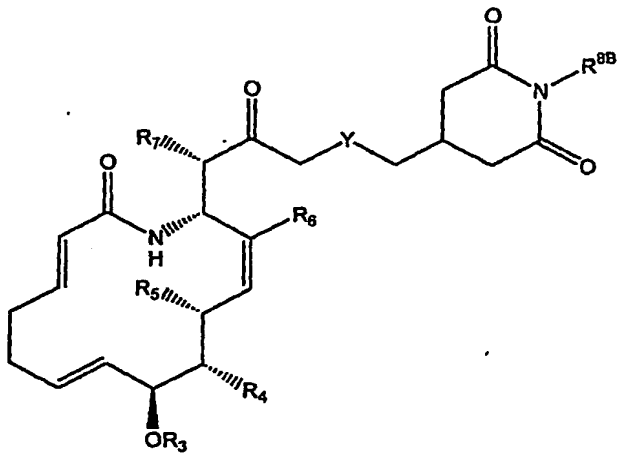
wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and Y is $-CHOR^{Y1}$, $-CHNR^{Y1}R^{Y2}$, C=O, C=S, $C=N(R^{Y1})$ or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, Y is –CHOH, $-CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0146] ***XII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



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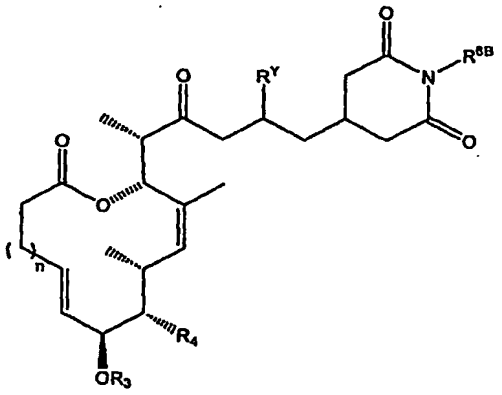
wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and Y is $-CHOR^{Y1}$, $-CHNR^{Y1}R^{Y2}$, C=O, C=S, $C=N(R^{Y1})$ or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, Y is –CHOH, $-CHNH_2$ or –CHF. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0147] ***XIII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein n, R_3 and R_4 are as defined in classes and subclasses herein; R^{8B} is hydrogen or lower alkyl; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are

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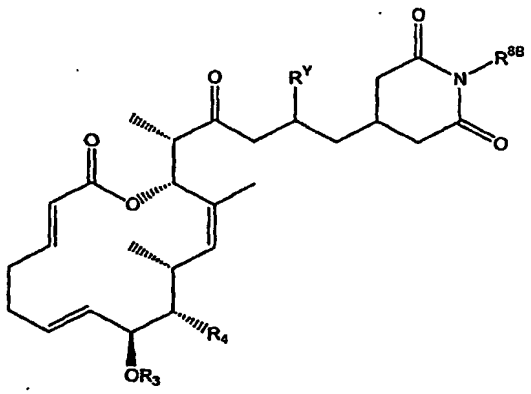
independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R^Y is OH, NH_2 or halogen (e.g., F). In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0148] ***XIV) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein R_3 and R_4 are as defined in classes and subclasses herein; R^{8B} is hydrogen or lower alkyl; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to

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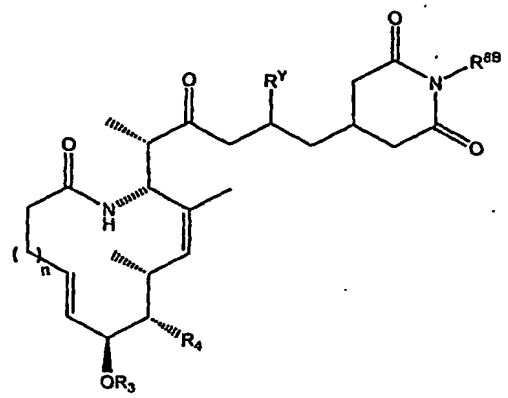
which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R^Y is OH, NH_2 or halogen (e.g., F). In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0149] ***XV) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***



wherein n, R_3 and R_4 are as defined in classes and subclasses herein; R^{8B} is hydrogen or lower alkyl; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R^Y is OH, NH_2 or halogen (e.g., F). In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

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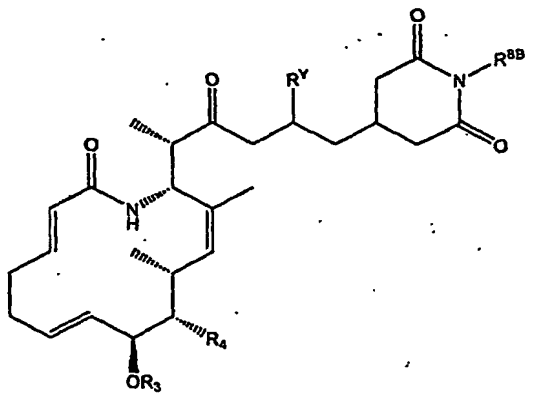
[0150] *XVI) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*



wherein R_3 and R_4 are as defined in classes and subclasses herein; R^{8B} is hydrogen or lower alkyl; and R^{Y} is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R^{Y} is OH, NH_2 or halogen (e.g., F). In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0151] *XVII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*

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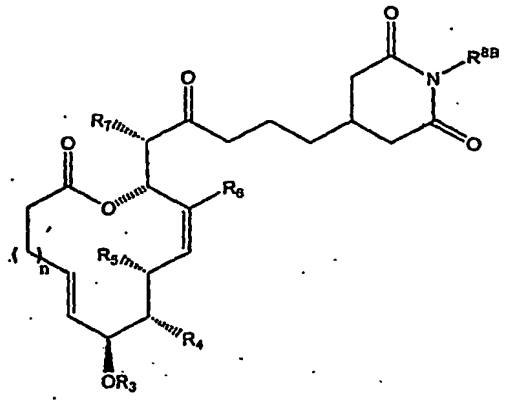

wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0152] ***XVIII) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***

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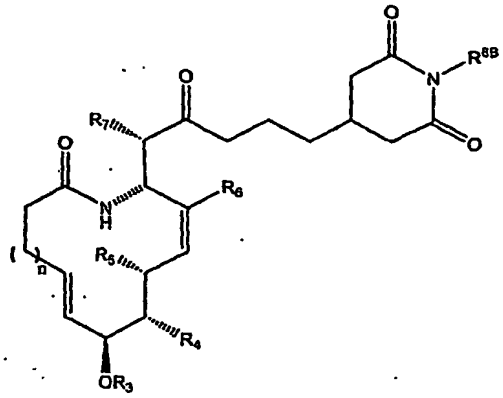

wherein R_3-R_6 and n are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0153] ***XIX) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):***

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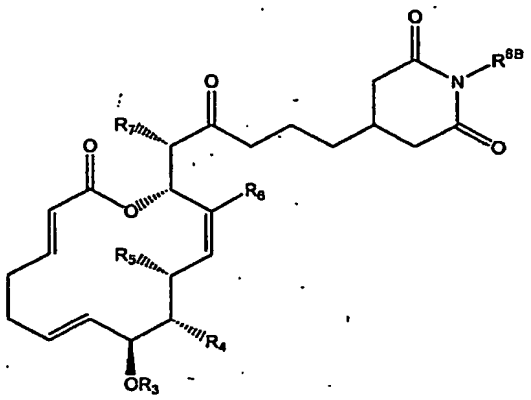

wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0154] *XX) Compounds of the formula (and pharmaceutically acceptable derivatives thereof):*

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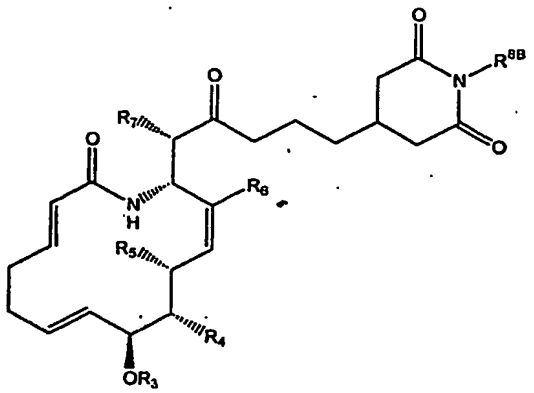

wherein R_3-R_6 are as defined in classes and subclasses herein; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl. In certain embodiments, R_3 is hydrogen, lower alkyl or an oxygen protecting group. In certain exemplary embodiments, R_3 is methyl. In certain other embodiments, R_5 and R_6 are independently lower alkyl. In certain exemplary embodiments, R_5 and R_6 are each methyl. In certain embodiments, n is 3. In certain embodiments, R_4 is halogen, hydroxyl, lower alkoxy or $NR^{4A}R^{4B}$, wherein R^{4A} and R^{4B} are independently hydrogen, lower alkyl, aryl, acyl or a nitrogen protecting group, or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a substituted or unsusbstituted heterocyclic or heteroaryl moiety. In certain embodiments, R_4 is a halogen selected from fluorine, chlorine, bromine and iodine. In certain exemplary embodiments, R_4 is fluorine. In certain other embodiments, R_4 is F, OH or NH_2. In certain other embodiments, R_7 is methyl. In certain other embodiments, R^{8B} is hydrogen, methyl or ethyl.

[0155] It will also be appreciated that for each of the subgroups **I-XX** described above, a variety of other subclasses are of special interest, including, but not limited to those classes described above i)-lxxxvii) and classes, subclasses and species of compounds described above and in the examples herein.

[0156] Some of the foregoing compounds can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, stereoisomers and/or diastereomers. Thus, inventive compounds and pharmaceutical compositions thereof may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of

stereoisomers. In certain embodiments, the compounds of the invention are enantiopure compounds. In certain other embodiments, mixtures of stereoisomers or diastereomers are provided.

[0157] Furthermore, certain compounds, as described herein may have one or more double bonds that can exist as either the Z or E isomer, unless otherwise indicated. The invention additionally encompasses the compounds as individual isomers substantially free of other isomers and alternatively, as mixtures of various isomers, *e.g.*, racemic mixtures of stereoisomers. In addition to the above-mentioned compounds *per se*, this invention also encompasses pharmaceutically acceptable derivatives of these compounds and compositions comprising one or more compounds of the invention and one or more pharmaceutically acceptable excipients or additives.

[0158] Compounds of the invention may be prepared by crystallization of compound of formula (I) under different conditions and may exist as one or a combination of polymorphs of compound of general formula (I) forming part of this invention. For example, different polymorphs may be identified and/or prepared using different solvents, or different mixtures of solvents for recrystallization; by performing crystallizations at different temperatures; or by using various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffractogram and/or other techniques. Thus, the present invention encompasses inventive compounds, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.

[0159] As discussed above, this invention provides novel compounds with a range of biological properties. Preferred compounds of this invention have biological activities relevant for the treatment of cancer and angiogenesis-related disorders.

[0160] Compounds of this invention include those specifically set forth above and described herein, and are illustrated in part by the various classes, subgenera and species disclosed elsewhere herein.

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[0161] Additionally, the present invention provides pharmaceutically acceptable derivatives of the inventive compounds, and methods of treating a subject using these compounds, pharmaceutical compositions thereof, or either of these in combination with one or more additional therapeutic agents. Certain compounds of the present invention are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference. Furthermore, it will be appreciated by one of ordinary skill in the art that the synthetic methods, as described herein, utilize a variety of protecting groups. It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example of proliferative disorders, including, but not limited to cancer. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to

be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0162] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or a prodrug or other adduct or derivative of a compound of this invention which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0163] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of amines, carboxylic acids, and other types of compounds, are well known in the art. For example, S.M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences, 66*: 1-19 (1977), incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting a free base or free acid function with a suitable reagent, as described generally below. For example, a free base function can be reacted with a suitable acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may, include metal salts such as alkali metal salts, *e.g.* sodium or potassium salts; and alkaline earth metal salts, *e.g.* calcium or magnesium salts. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate,

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hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

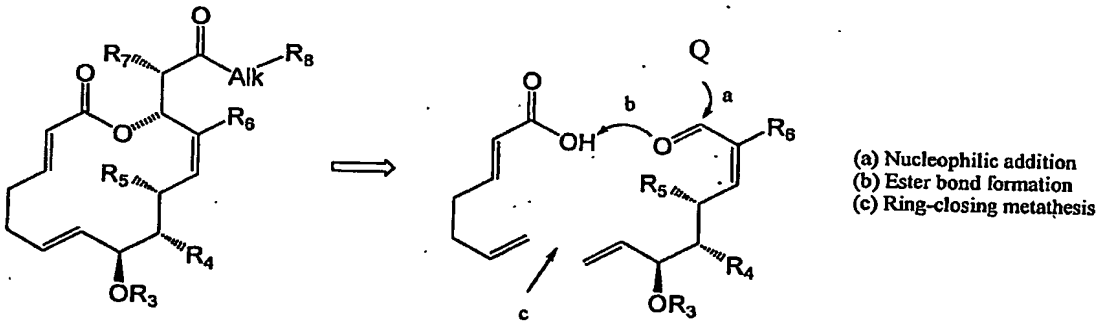
[0164] Additionally, as used herein, the term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moeity advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

[0165] Furthermore, the term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the issues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0166] **2) Synthetic Methodology**

[0167] In another aspect, the present invention provides methods for preparing novel macrocycles having formula (I) a described above and in certain classes and subclasses herein. An overview of exemplary synthesic approaches to the inventive compounds is provided below, as detailed in Schemes 1-15, and in the Exemplification herein. It will be appreciated that the methods as described herein can be applied to each of the compounds as disclosed herein and equivalents thereof. Additionally, the reagents and starting materials are well known to those skilled in the art. Although the following schemes describe certain exemplary compounds, it will be appreciated that the use of alternate starting materials will yield other analogs of the invention. For example, compounds are described below where X is O; however, it will be appreciated that alternate starting materials and/or intermediates can be utilized to generate compounds where X is NH, N-alkyl, S, CH_2, etc.

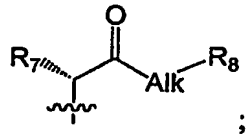
[0168] In certain embodiments, compounds as provided herein, especially those where n is 3, X is O, and R_1 and R_2 are each hydrogen, are prepared from assembly of three segments, as depicted in Scheme 1 below:



A

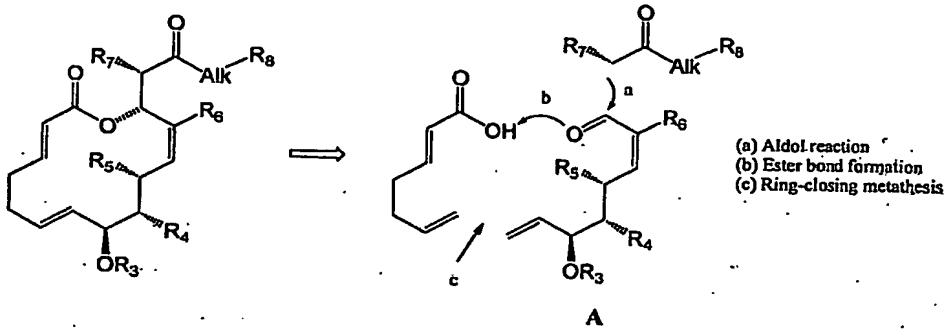
Scheme 1

[0169] In certain embodiments, compounds of the invention where Q is a carbonyl-containing moiety having the structure:



;

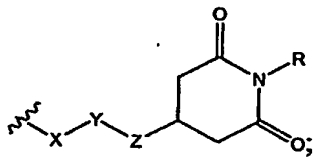
are prepared from assembly of three segments, as depicted in Scheme 2 below:



A

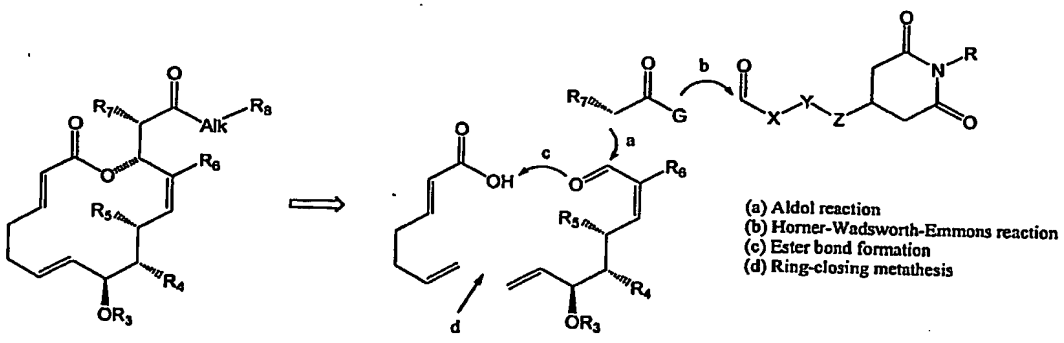
Scheme 2

[0170] In certain embodiments, compounds where –Alk-R_8 represents a glutarimide-containing side chain, having the structure:



wherein X, Y, Z and R are as defined in classes and subclasses herein;

are prepared from assembly of three segments, as depicted in Scheme 3 below:



A

Scheme 3

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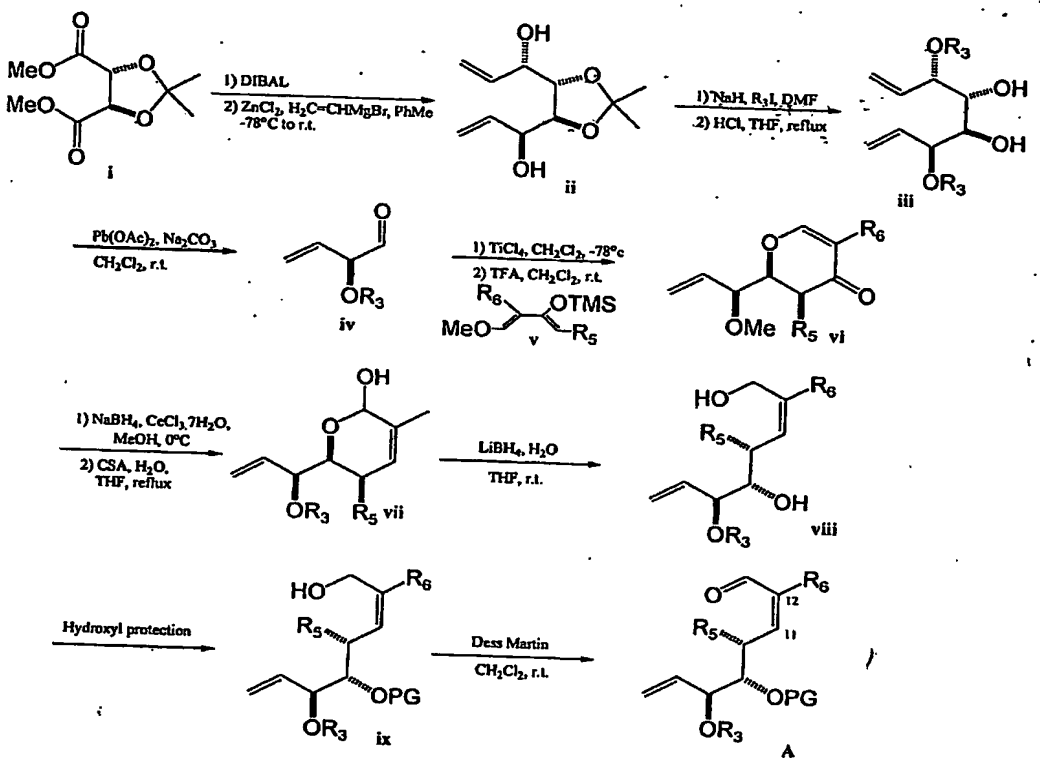
wherein G represents a group suitable for effecting the Horner-Wadsworth-Emmons-type coupling.

[0171] In certain embodiments, the preparation of fragment A may be accomplished as depicted in Scheme 4 below:



Scheme 4

[0172] For example, reduction of commercially available dimethyl 2,3-*O*-isopropylidene-L-tartrate **i**, followed by diastereoselective divinylzinc addition to the *in situ* generated dialdehyde produces the desired vinyl carbinol **ii** (see, Jorgensen *et al.*, *J. Org. Chem.*, **2001**, *66*, 4630). Alkylation (or arylation) of the two hydroxyl groups and removal of the acetonide protecting group yields diol **iii**. Glycol cleavage of **iii** affords α-alkoxy-β-vinyl aldehyde **iv**. Subjecting **iv** to a Lewis acid catalyzed diene aldehyde condensation (LACDAC) sequence with the synergistically activated diene **v** in the presence of $TiCl_4$, yields the α-chelation controlled

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dihydropyrone **vi** (for chelation-controlled cyclocondensations of α-alkoxy aldehydes with synergistically activated dienes, see: Danishefsky *et al.*, *J. Am. Chem. Soc.*, **1985**, *107*, 1256). The cyclocondensation allows the construction of the three contiguous stereocenters of the macrolide and sets the stage for establishing the trisubstituted (*Z*)-alkene C11-C12. Luche reduction of enone **vi** affords the corresponding allylic alcohol, which can be made to undergo an aqueous Ferrier rearrangement to give alcohol **vii** (for a reference on the Luche reduction, see: Luche *et al.*, *J. Am. Chem. Soc.*, **1979**, *101*, 5848; for a reference on the Ferrier rearrangement, see: Ferrier, *J. Chem. Soc.*, **1964**, 5443). Reductive opening of lactol **vii**, protection of the secobdary hydroxyl group, and oxidation of the primary alcohol yields the C7-C13 core fragment **A**.

[0173] One of ordinary skill in the art will recognize that the protected hydroxyl (OPG) may be converted to a variety of functional groups, including, but not limited to OH, NH_2 and F, thus allowing access to compounds where R_4 is OH, NH_2 or F, among others.

[0174] In certain embodiments, coupling of fragment A with a glutarimide moiety may be accomplished as exemplified in Scheme 5 below:

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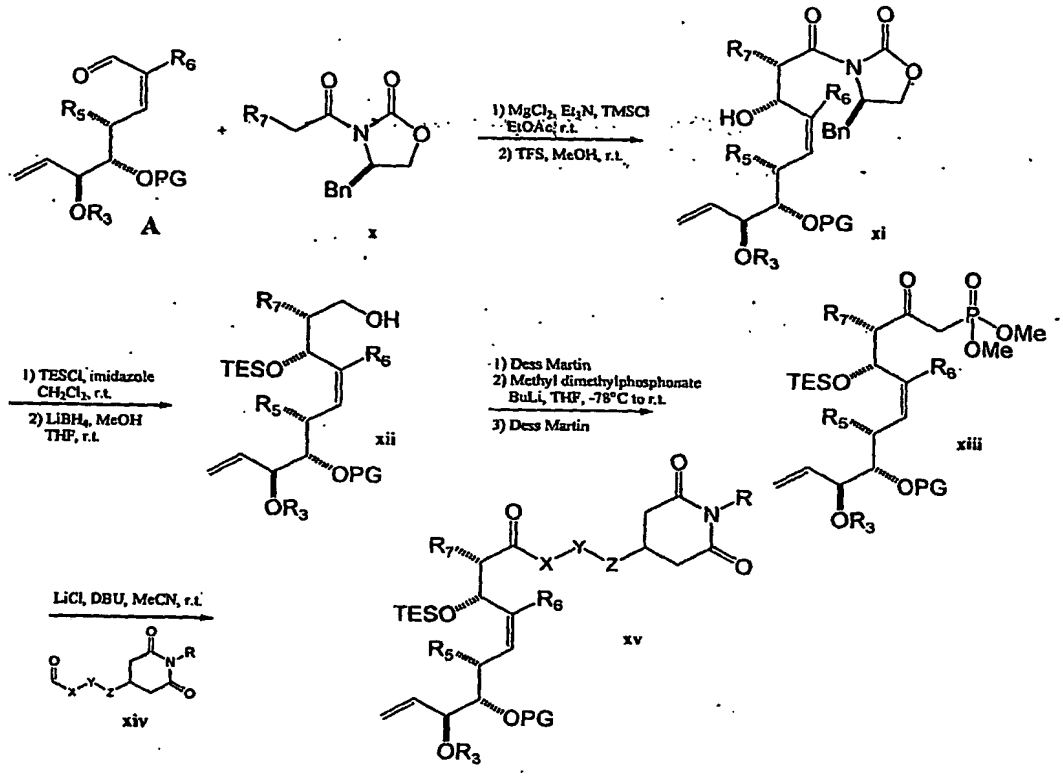

Scheme 5

[0175] For example, Addition of x to fragment A in the presence of $MgCl_2$ and TMSCl produces alcohol **xi** (for a reference reporting a suitable protocol for anti-selective aldol coupling, see: Evans *et al.*, *J. Am. Chem. Soc.*, **2002**, *124*, 392). Protection of the resulting secondary hydroxyl group and reductive cleavage of the chiral auxiliary affords alcohol **xii**. Coupling of compound **xii** with the glutarimide side chain may be effected, for example, via a Horner-Wadsworth-Emmons reaction. For example, the Masamune-Roush variant of the Horner-Wadsworth-Emmons reaction may be used (see: Blanchette *et al.*, *Tet. Lett.*, **1984**, *25*, 2183). Thus, conversion of **xii** via an oxidation/nucleophilic addition/oxidation sequence gives β-ketophosphonate **xiii**. Treatment of the phosphonate with LiCl and DBU in the presence of glutarimide aldehyde **xiv** results in efficient formation of the desired enone **xv**.

[0176] In certain embodiments, formation of the macrolide ring is effected as shown in Scheme 6 below:

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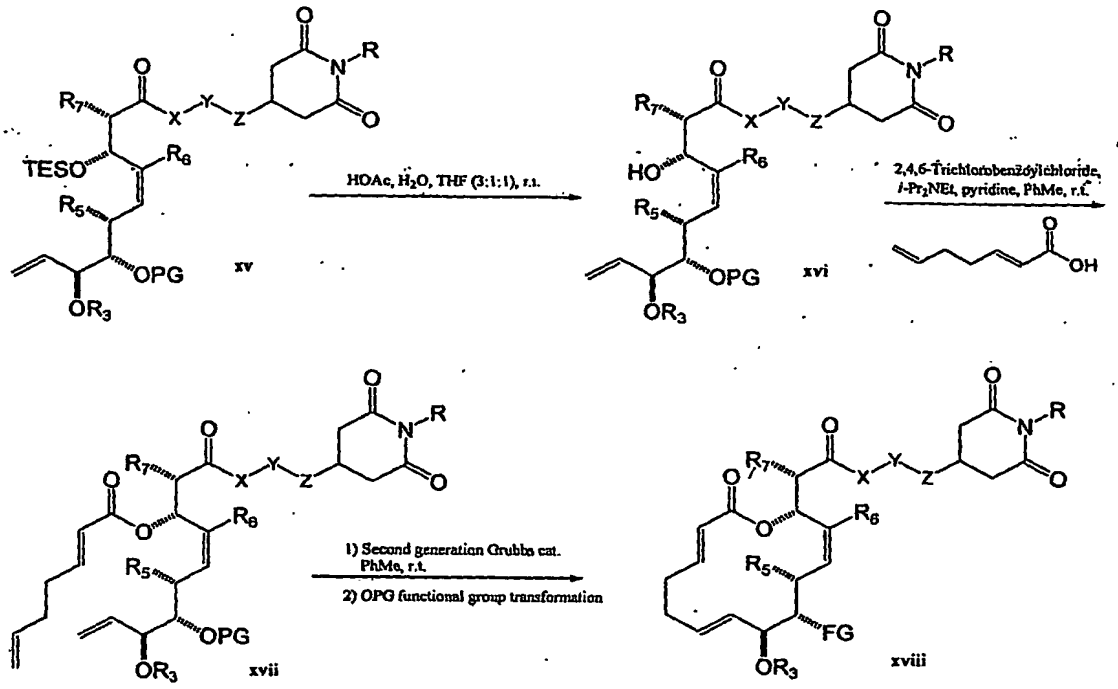

Scheme 6

[0177] For example, removal of the TES protecting group of enone **xv** yields seco-alcohol **xvi**. A variety of methods for effecting acylation of **xvi** with dienoic acid may be utilized. For example, a modified Yamaguchi procedure may be used to give the metathesis precursor **xvii** (see, Inanaga *et al.*, *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1989; and Song *et al.*, *Org. Lett.*, **2002**, *4*, 647). A variety of methods for effecting ring-closure metathesis of **xvii** to the desired (*E*)-isomer may be utilized. For example, subjecting tetraene **xvii** to ring-closure metathesis conditions using the second generation Grubbs catalyst gives the desired macrocyclic (*E*)-isomer **xviii** in high yield (see, Scholl *et al.*, *Org. Lett.*, **1999**, *1*, 953).

[0178] Methods for converting the protected hydroxyl group (OPG) into a variety of functionalities are known in the art. The practitioner skilled in the relevant art will know how to select reagents and reaction conditions to effect transformation of the protected hydroxyl group (OPG) into a desired functionality FG. In certain embodiments, FG represents OH, NH_2 or halogen (e.g., F).

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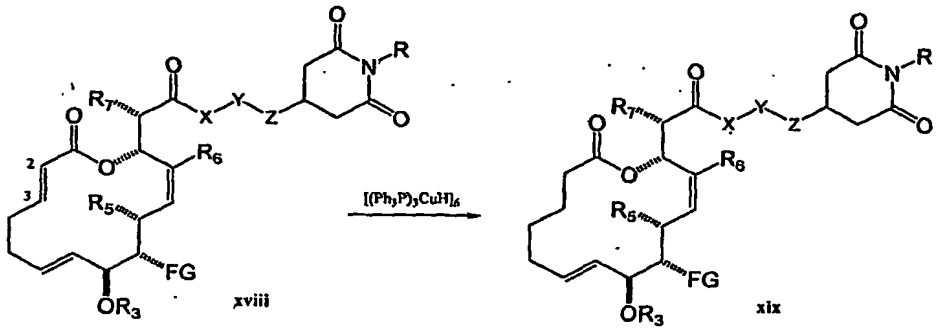
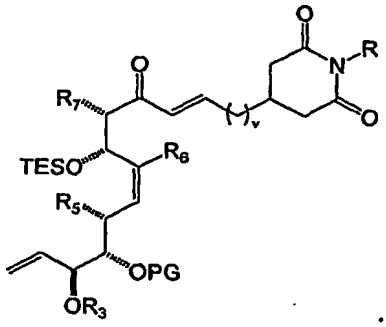
[0179] In certain other embodiments, the conjugate ester group present in compound **xviii** (*i.e.*, at C_2-C_3) may be reduced to the corresponding saturated ester **xix**. The practitioner skilled in the relevant art will know how to select reagents and reaction conditions to effect this transformation. For example, the Stryker copper hydride may be used (see, Mahoney *et al.*, *J. Am. Chem. Soc.*, **1988**, *110*, 291), as depicted in Sheme 7 below:



Scheme 7

[0180] In certain embodiments, in Schemes 5-7 above, -X-Y-Z- represents –CH=CH-$(CH_2)_v$- where v is an integer from 1-4. Thus, compound **xv** depicted in scheme 5 may have the following structure (**xv**[a]):



(**xv**[a])

[0181] In certain embodiments, conjugate reduction of this intermediate may be effected using the stryker reagent, as shown in scheme 8 below:

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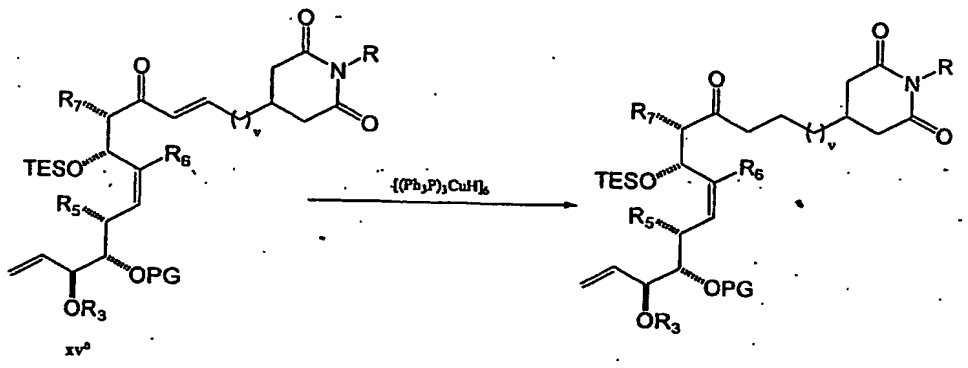
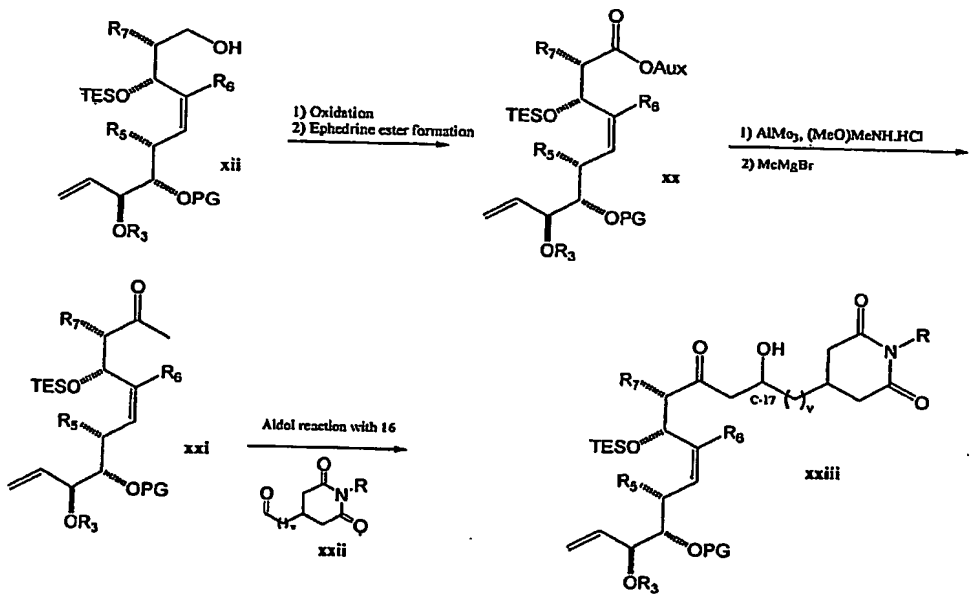


Scheme 8

[0182] In certain other embodiments, where further functionalization at C_{17} of the alkyl-glutarimide side chain of **xv**^{a} is desired, coupling of fragment **xii** with a glutarimide moiety may be accomplished as shown in Scheme 9 below:



Scheme 9

[0183] For example, ephedrine ester **xx** may be converted to the corresponding Weinreb amide, which is then transformed into the corresponding methyl ketone upon treatment with MeMgBr. Aldol reaction of ketone **xxi** with protected glutarimide aldehyde **xxii** yields the

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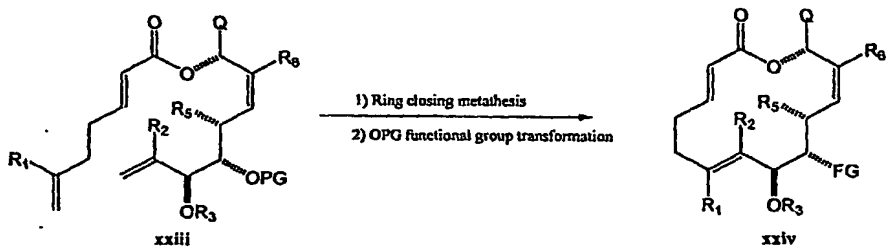
formation of the C_{17}-hydroxylated adduct **xxiii**. The practitioner skilled in the relevant art will know how to select reagents and reaction conditions to effect transformation of this C-17 hydroxyl group into functionalities of interest (*e.g.*, alkoxyl, aryloxy, NH_2 or halogen (*e.g.*, F)).

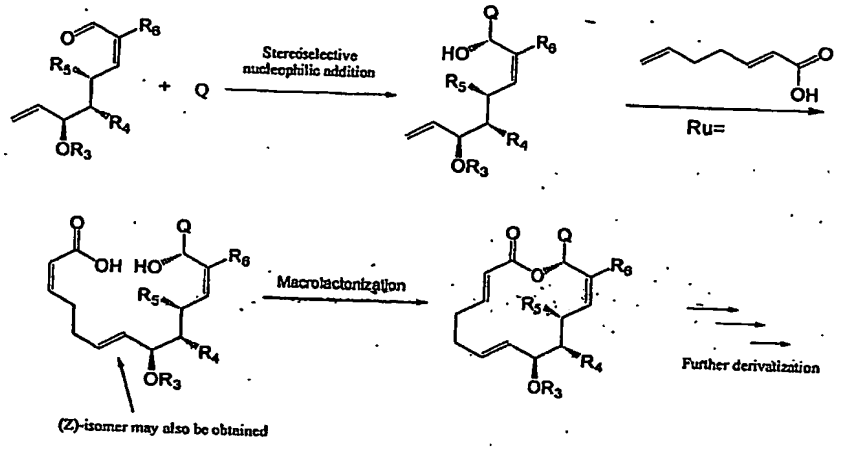
[0184] One of ordinary skill in the art will recognize that the ring closing metathesis coupling may be effected with fragments where at least one of R_1 and R_2 is not hydrogen, to introduce functionalization at C_6 and/or C_7, as shown in Scheme 10 below. In addition, metathesis reaction conditions may be adjusted so that the (*Z*)-isomer is predominantly formed, rather than the (*E*)-isomer.



xxiii xxiv

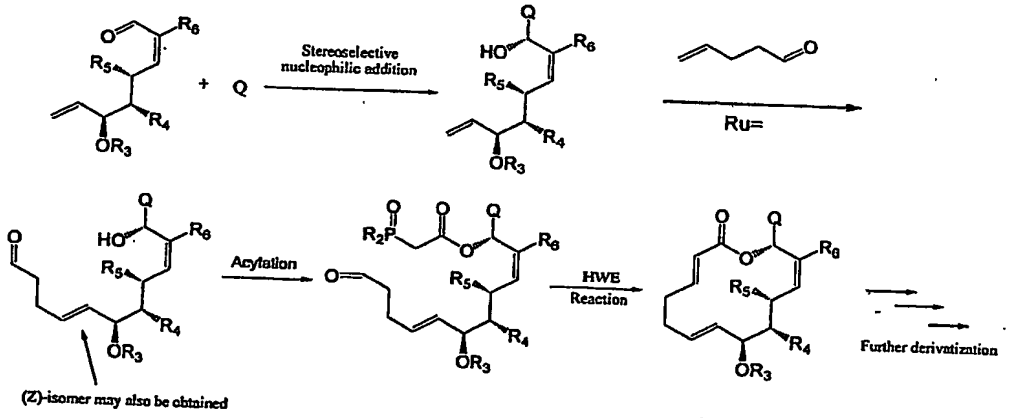
Scheme 10

[0185] One of ordinary skill in the art will also recognize that the inventive methods for assembling the macrocyclic structure are not limited by the order in which the different fragments may be put together. Exemplary synthetic approaches were described in Schemes 1-10 above, whereby the inventive compounds are prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) ester bond formation between the A-Q adduct with a suitable dienoic acid and (iii) ring closing ring closure to give the desired macrocyclic scaffold. Other approaches may be used. For example, inventive compounds may be prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) cross-metathesis reaction of the A-Q adduct obtained in (i) with a suitable dienoic acid and (iii) macrolactonization (*i.e.*, intramolecular ester bond formation) to give the desired macrocyclic scaffold (See Scheme 11).



Scheme 11

[0186] Alternatively, inventive compounds may be prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) cross-metathesis reaction of the A-Q adduct obtained in (i) with a suitable enone, (iii) acylation of the adduct obtained in (ii) with a suitable reagent and (iv) intramolecular Horner-Wadsworth-Emmons olefination to give the desired macrocyclic scaffold (See Scheme 12).



Scheme 12

[0187] In certain embodiments, the invention provides methods of preparing compounds where X_1 is NH. Schemes 1-12 above detail exemplary synthetic approaches for preparing

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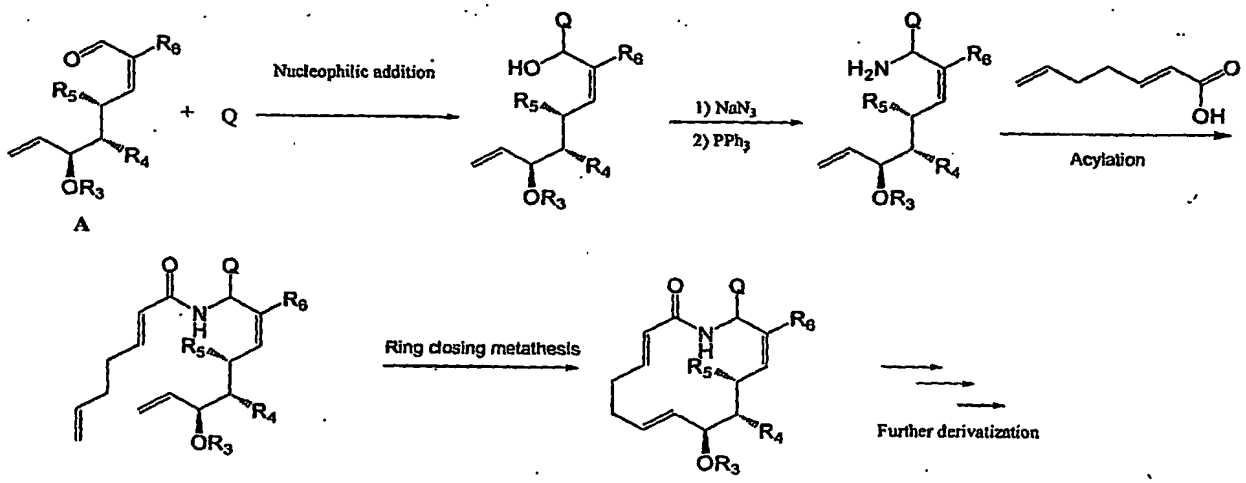
inventive compounds where X_1 is O. A similar approach may be used to access compounds where X_1 is NH (*i.e.*, macrolactams). For example, inventive compounds may be prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) conversion of the resulting alcohol to an amine, (iii) amide bond formation between the A-Q adduct formed in (ii) with a suitable dienoic acid and (iv) ring closing metathesis to give the desired macrolactam scaffold (Scheme 13).



Scheme 13

[0188] In certain embodiments, inventive compounds may be prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) conversion of the resulting alcohol to the corresponding amine, (iii) cross-metathesis reaction of the A-Q adduct obtained in (ii) with a suitable dienoic acid and (iv) intramolecular amide bond formation to give the desired macrolactam scaffold (See Scheme 14).

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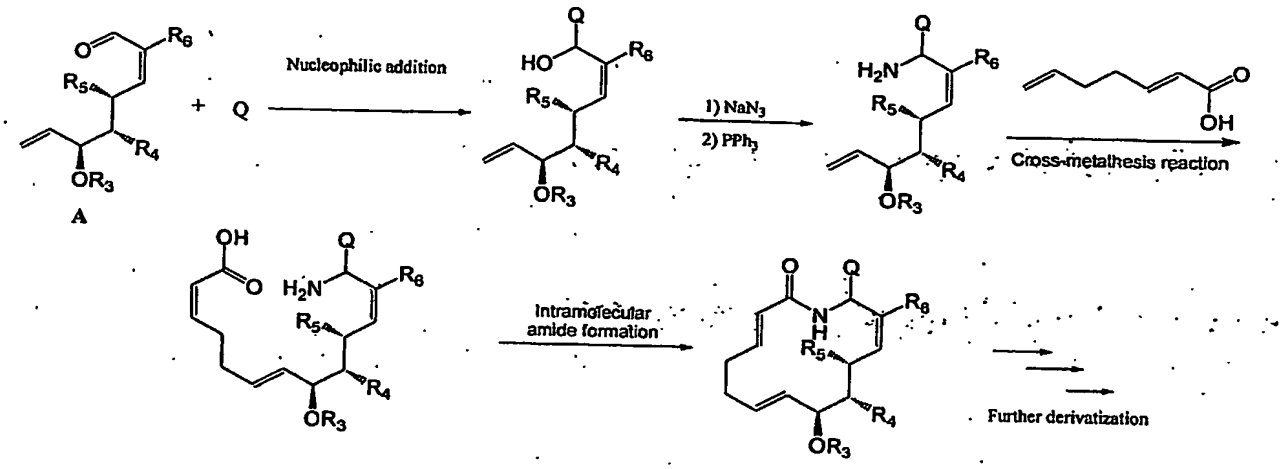
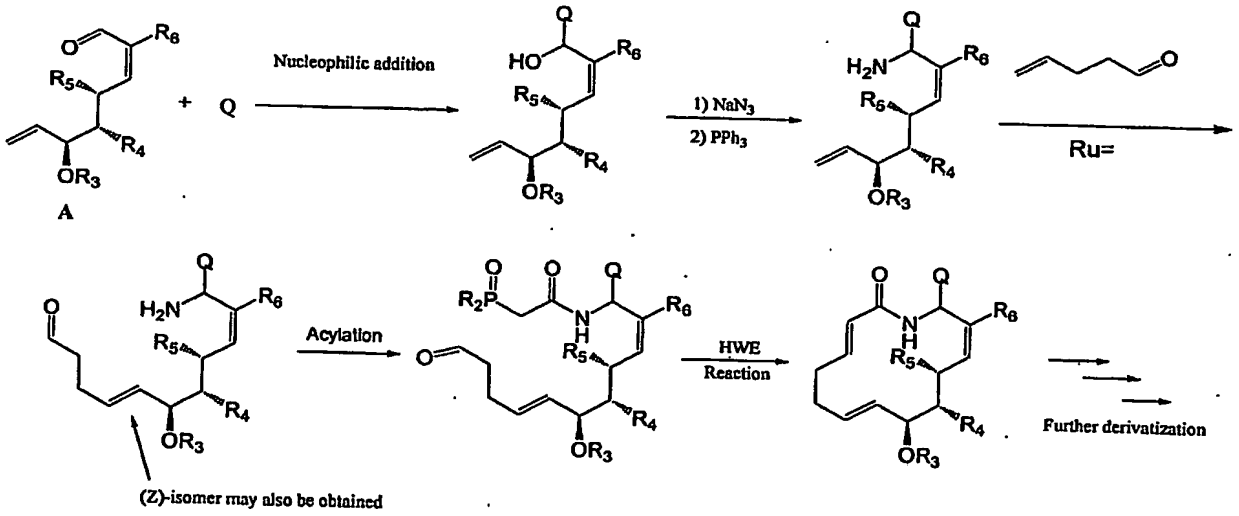


Scheme 14

[0189] Alternatively, inventive compounds may be prepared by (i) nucleophilic addition of Q on fragment A, followed by (ii) conversion of the resulting alcohol to the corresponding amine, (iii) cross-metathesis reaction of the A-Q adduct obtained in (ii) with a suitable enone, (iv) acylation of the adduct obtained in (iii) with a suitable reagent and (v) intramolecular Horner-Wadsworth-Emmons olefination to give the desired macrocyclic scaffold (See Scheme 15).



Scheme 15

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[0190] Other approaches to prepare inventive compounds will be readily apparent to the practitioner skilled in the relevant art.

[0191] Diversification:

[0192] It will also be appreciated that each of the components used in the synthesis of Migrastatin analogues can be diversified either before synthesis or alternatively after the construction of the macrocycle. As used herein, the term "diversifying" or "diversify" means reacting an inventive compound (I) or any of the precursor fragments (*e.g.*, (A) etc.) as defined herein (or any classes or subclasses thereof) at one or more reactive sites to modify a functional moiety or to add a functional moiety (*e.g.*, nucleophilic addition of a substrate). Described generally herein are a variety of schemes to assist the reader in the synthesis of a variety of analogues, either by diversification of the intermediate components or by diversification of the macrocyclic structures as described herein, and classes and subclasses thereof. It will also be appreciated that although many of the schemes herein depict 14-membered macrocycles, the reactions described herein may also be applied to other ring structures (for example to 12-, 13- and 15-membered ring structures). It will be appreciated that a variety of diversification reactions can be employed to generate novel analogues. As but a few examples, epoxidation and aziridation can be conducted to generate epoxide and aziridine analogues of compounds described herein. Additionally, addition across either double bond will generate additional diversity. In addition to diversification after macrocyclization, it will be understood that diversification can occur prior to macrocyclization (*e.g.*, epoxidation, aziridation, reduction at a C_{2-3} and/or C_{12-13} double bond(s) could occur prior to metathesis ring-closure, or other means known in the art to effect macorcyclic ring closure, to describe just one example). For additional guidance available in the art, the practitioner is directed to "Advanced Organic Chemistry", March, J. John Wiley & Sons, 2001, 5th ed., the entire contents of which are hereby incorporated by reference.

[0193] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:

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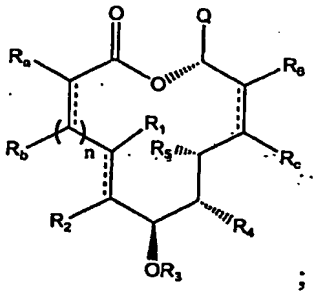
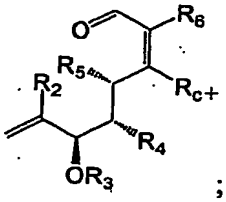


;

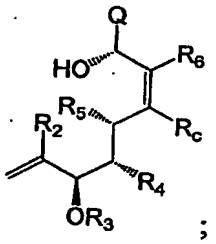
said method comprising steps of:

a. reacting a fragment Q with a compound having the structure:



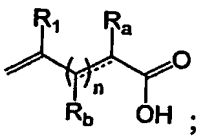
;

under suitable conditions to effect formation of an A-Q adduct having the structure:



;

b. reacting A-Q formed in step a with a dienoic acid having the structure:



;

under suitable conditions to effect formation of an ester having the structure:

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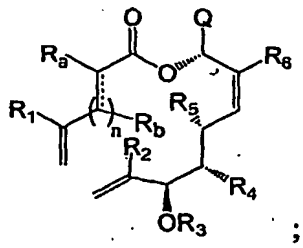
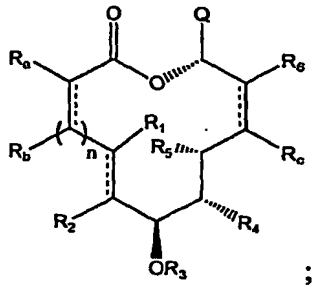


; and

c. subjecting the ester formed in step b to ring closing metathesis reaction conditions to effect formation of the macrolide having the structure:



;

wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

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R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with R_c, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

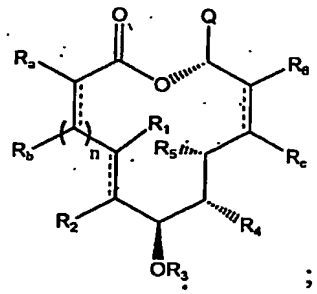
n is an integer from 1 to 5; and

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

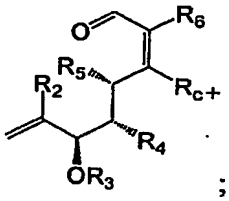
[0194] In certain embodiments, the method further comprises steps of diversifying the macrolide obtained in step c to form a Migrastatin analog with the desired functionalization.

[0195] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:

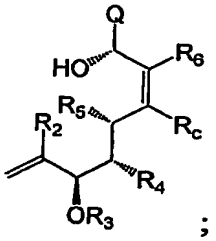


said method comprising steps of:

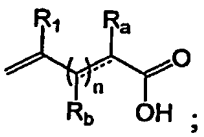
a. reacting a fragment Q with a compound having the structure:



under suitable conditions to effect formation of an A-Q adduct having the structure:



b. reacting A-Q formed in step a with a dienoic acid having the structure:



under suitable conditions to effect formation of an olefin having the structure:

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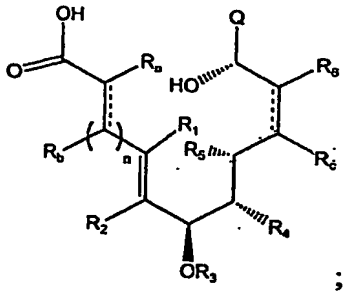
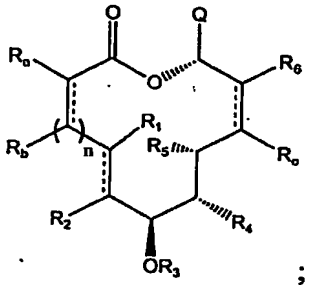


c. subjecting the olefin formed in step b to suitable conditions to effect formation of the macrolide having the structure:



wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5; and

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

[0196] In certain embodiments, the method further comprises steps of diversifying the macrolide obtained in step c to form a Migrastatin analog with the desired functionalization.

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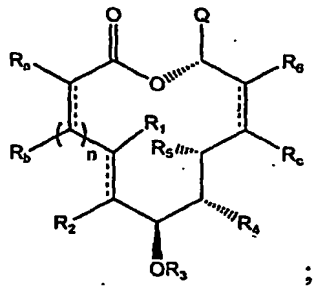
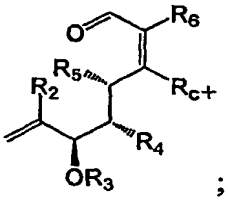
[0197] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:



;

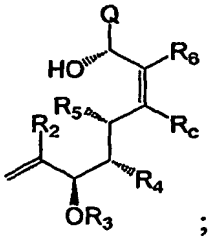
said method comprising steps of:

a. reacting a fragment Q with a compound having the structure:



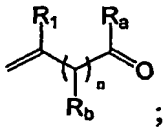
;

under suitable conditions to effect formation of an A-Q adduct having the structure:



;

b. reacting A-Q formed in step a with n enone having the structure:



;

under suitable conditions to effect formation of an olefin having the structure:

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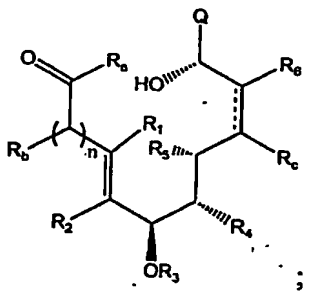
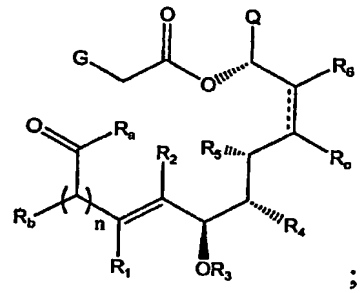
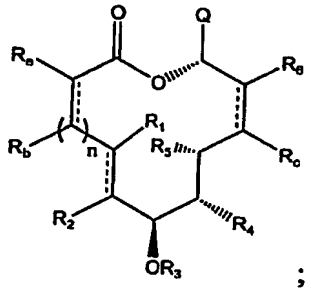


c. acylating the olefin formed in step b with a suitable reagent under suitable conditions to effect formation of an intermediate having the structure:



wherein G is a group suitable to effect ring closure; and

d. subjecting the intermediate formed in step c to suitable conditions to effect formation of the macrolide having the structure:



wherein $\mathbf{R_1}$ and $\mathbf{R_2}$ are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently

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hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

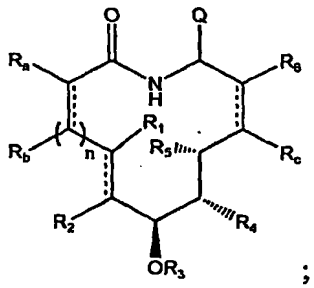
n is an integer from 1 to 5; and

Q is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{Q1}$, -NO_2, -COR^{Q1}, -CO_2R^{Q1}, -$NR^{Q1}C(=O)R^{Q2}$, -$NR^{Q1}C(=O)OR^{Q2}$, -$CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{Q1}; wherein W is independently -O-, -S- or -NR^{Q3}-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

[0198] In certain embodiments, G is –$P(=O)R'_2$ and step d involves subjecting the intermediate formed in step c to Horner-Wadsworth-Emmons reaction conditions to effect formation of the macrolide. In certain other embodiments, the method further comprises steps of diversifying the macrolide obtained in step d to form a Migrastatin analog with the desired functionalization.

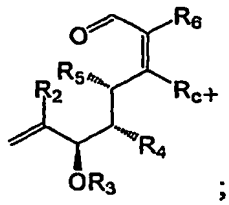
[0199] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:



;

said method comprising steps of:

a. reacting a fragment Q with a compound having the structure:



;

under suitable conditions to effect formation of an alcohol adduct having the structure:

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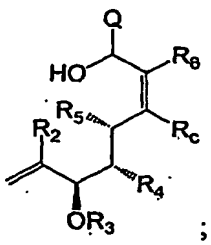
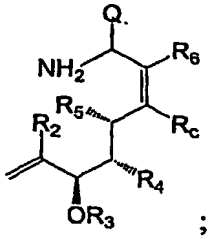


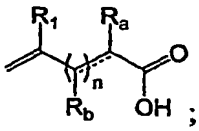
;

b. converting the alcohol adduct formed in step a under suitable conditions to form an amine having the structure:



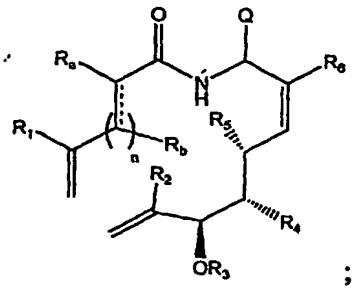
;

c. reacting the amine formed in step b with a dienoic acid having the structure:



;

under suitable conditions to effect formation of an amide having the structure:



; and

d. subjecting the amide formed in step c to ring closing metathesis reaction conditions to effect formation of the macrolide having the structure:

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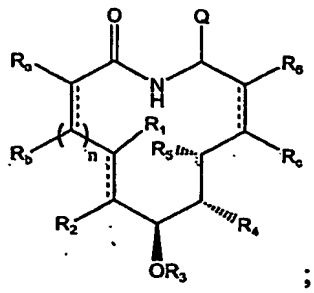

wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is

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independently -O-, -S- or -NR^{a3}-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{c1}$, -NO_2, -COR^{c1}, -CO_2R^{c1}, -$NR^{c1}C(=O)R^{c2}$, -$NR^{c1}C(=O)OR^{c2}$, -$CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{c1}; wherein W is independently -O-, -S- or -NR^{c3}-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

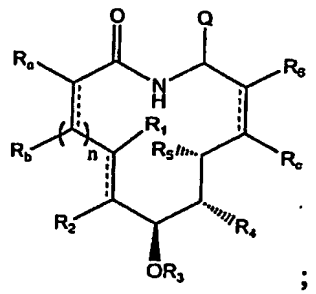
n is an integer from 1 to 5;

Q is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{Q1}$, -NO_2, -COR^{Q1}, -CO_2R^{Q1}, -$NR^{Q1}C(=O)R^{Q2}$, -$NR^{Q1}C(=O)OR^{Q2}$, -$CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{Q1}; wherein W is independently -O-, -S- or -NR^{Q3}-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

[0200] In certain embodiments, the method further comprises steps of diversifying the macrolide obtained in step d to form a macrolactam (*i.e.*, Migrastatin analog) with the desired functionalization.

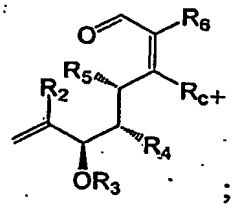
[0201] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:



;

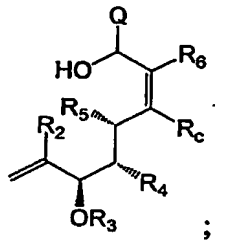
said method comprising steps of:

b. reacting a fragment Q with a compound having the structure:



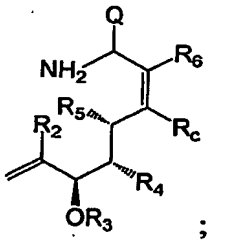
;

under suitable conditions to effect formation of an alcohol adduct having the structure:



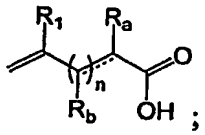
;

b. converting the alcohol adduct formed in step a under suitable conditions to form an amine having the structure:



;

d. reacting the amine formed in step b with a dienoic acid having the structure:



;

under suitable conditions to effect formation of an olefin having the structure:

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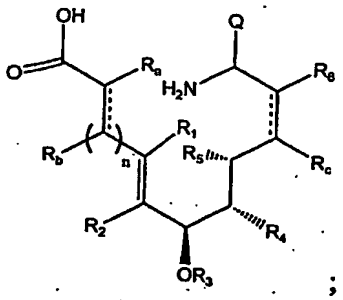
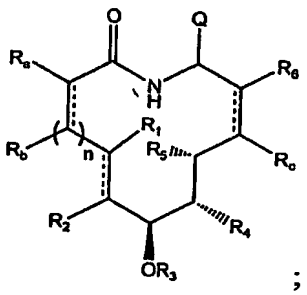


; and

e. subjecting the olefin formed in step c to suitable conditions to effect formation of the macrolactam having the structure:



;

wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

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R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

[0202] In certain embodiments, the method further comprises steps of diversifying the macrolide obtained in step e to form a macrolactam (*i.e.*, Migrastatin analog) with the desired functionalization.

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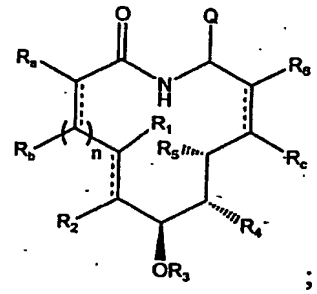
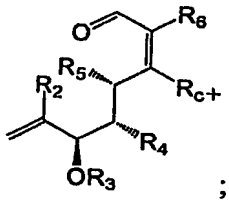
[0203] In certain embodiments, the present invention provides a method for preparing a Migrastatin analog having the structure:

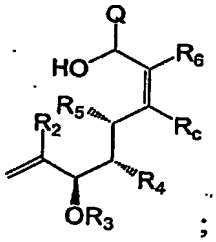


said method comprising steps of:

a. reacting a fragment Q with a compound having the structure:



under suitable conditions to effect formation of an A-Q adduct having the structure:



b. converting the alcohol adduct formed in step a under suitable conditions to form an amine having the structure:

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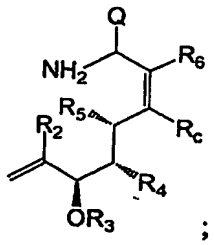
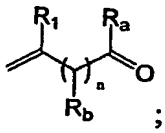


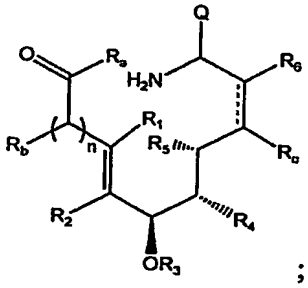
;

c. reacting the amine formed in step b with an enone having the structure:



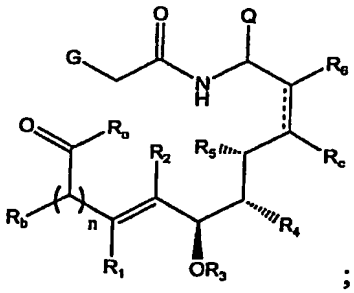
;

under suitable conditions to effect formation of an olefin having the structure:



;

d. acylating the olefin formed in step c with a suitable reagent under suitable conditions to effect formation of an intermediate having the structure:



;

wherein G is a group suitable to effect ring closure; and

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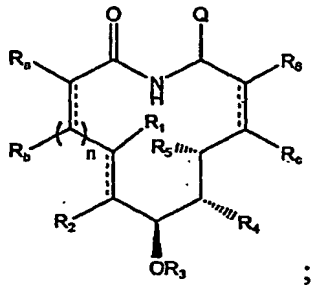
e. subjecting the intermediate formed in step d to suitable conditions to effect formation of the macrolide having the structure:



;

wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5; and

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

[0204] In certain embodiments, G is $-P(=O)R'_2$ and step e involves subjecting the intermediate formed in step d to Horner-Wadsworth-Emmons reaction conditions to effect formation of the macrolide. In certain other embodiments, the method further comprises steps of diversifying the macrolide obtained in step e to form a Migrastatin analog with the desired functionalization.

[0205] **3) Pharmaceutical Compositions**

[0206] In another aspect of the present invention, pharmaceutical compositions are provided, which comprise any one of the compounds described herein (or a prodrug, pharmaceutically acceptable salt or other pharmaceutically acceptable derivative thereof), and

optionally comprise a pharmaceutically acceptable carrier. In certain other embodiments, the compositions of the invention are useful for the treatment of cancer and disorders associated with metastasis and/or angiogenesis. In certain embodiments, the inventive compositions optionally further comprise one or more additional therapeutic agents. In certain other embodiments, the additional therapeutic agent is a cytotoxic agent, as discussed in more detail herein. In certain other embodiments, the additional therapeutic agent is an anticancer agent. Alternatively, a compound of this invention may be administered to a patient in need thereof in combination with the administration of one or more other therapeutic agents. For example, additional therapeutic agents for conjoint administration or inclusion in a pharmaceutical composition with a compound of this invention may be an antiangiogenesis agent or anticancer agent approved for the treatment of cancer, as discussed in more detail herein, or it may be any one of a number of agents undergoing approval in the Food and Drug Administration that ultimately obtain approval for the treatment of cancer.

[0207] As described above, the pharmaceutical compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatine; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil, sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl

laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogenfree water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0208] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0209] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0210] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0211] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension or crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include (poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissues.

[0212] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0213] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0214] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0215] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose and starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions, which can be used, include polymeric substances and waxes.

[0216] The present invention encompasses pharmaceutically acceptable topical formulations of inventive compounds. The term "pharmaceutically acceptable topical formulation", as used herein, means any formulation which is pharmaceutically acceptable for intradermal administration of a compound of the invention by application of the formulation to the epidermis. In certain embodiments of the invention, the topical formulation comprises a carrier system. Pharmaceutically effective carriers include, but are not limited to, solvents (*e.g.*,

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alcohols, poly alcohols, water), creams, lotions, ointments, oils, plasters, liposomes, powders, emulsions, microemulsions, and buffered solutions (*e.g.*, hypotonic or buffered saline) or any other carrier known in the art for topically administering pharmaceuticals. A more complete listing of art-known carriers is provided by reference texts that are standard in the art, for example, Remington's Pharmaceutical Sciences, 16th Edition, 1980 and 17th Edition, 1985, both published by Mack Publishing Company, Easton, Pa., the disclosures of which are incorporated herein by reference in their entireties. In certain other embodiments, the topical formulations of the invention may comprise excipients. Any pharmaceutically acceptable excipient known in the art may be used to prepare the inventive pharmaceutically acceptable topical formulations. Examples of excipients that can be included in the topical formulations of the invention include, but are not limited to, preservatives, antioxidants, moisturizers, emollients, buffering agents, solubilizing agents, other penetration agents, skin protectants, surfactants, and propellants, and/or additional therapeutic agents used in combination to the inventive compound. Suitable preservatives include, but are not limited to, alcohols, quaternary amines, organic acids, parabens, and phenols. Suitable antioxidants include, but are not limited to, ascorbic acid and its esters, sodium bisulfite, butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, and chelating agents like EDTA and citric acid. Suitable moisturizers include, but are not limited to, glycerine, sorbitol, polyethylene glycols, urea, and propylene glycol. Suitable buffering agents for use with the invention include, but are not limited to, citric, hydrochloric, and lactic acid buffers. Suitable solubilizing agents include, but are not limited to, quaternary ammonium chlorides, cyclodextrins, benzyl benzoate, lecithin, and polysorbates. Suitable skin protectants that can be used in the topical formulations of the invention include, but are not limited to, vitamin E oil, allatoin, dimethicone, glycerin, petrolatum, and zinc oxide.

[0217] In certain embodiments, the pharmaceutically acceptable topical formulations of the invention comprise at least a compound of the invention and a penetration enhancing agent. The choice of topical formulation will depend or several factors, including the condition to be treated, the physicochemical characteristics of the inventive compound and other excipients present, their stability in the formulation, available manufacturing equipment, and costs constraints. As used herein the term " penetration enhancing agent " means an agent capable of transporting a pharmacologically active compound through the stratum corneum and into the

epidermis or dermis, preferably, with little or no systemic absorption. A wide variety of compounds have been evaluated as to their effectiveness in enhancing the rate of penetration of drugs through the skin. See, for example, Percutaneous Penetration Enhancers, Maibach H. I. and Smith H. E. (eds.), CRC Press, Inc., Boca Raton, Fla. (1995), which surveys the use and testing of various skin penetration enhancers, and Buyuktimkin *et al.*, Chemical Means of Transdermal Drug Permeation Enhancement in Transdermal and Topical Drug Delivery Systems, Gosh T. K., Pfister W. R., Yum S. I. (Eds.), Interpharm Press Inc., Buffalo Grove, Ill. (1997). In certain exemplary embodiments, penetration agents for use with the invention include, but are not limited to, triglycerides (*e.g.*, soybean oil), aloe compositions (*e.g.*, aloe-vera gel), ethyl alcohol, isopropyl alcohol, octolyphenylpolyethylene glycol, oleic acid, polyethylene glycol 400, propylene glycol, N-decylmethylsulfoxide, fatty acid esters (*e.g.*, isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate) and N-methyl pyrrolidone.

[0218] In certain embodiments, the compositions may be in the form of ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. In certain exemplary embodiments, formulations of the compositions according to the invention are creams, which may further contain saturated or unsaturated fatty acids such as stearic acid, palmitic acid, oleic acid, palmito-oleic acid, cetyl or oleyl alcohols, stearic acid being particularly preferred. Creams of the invention may also contain a non-ionic surfactant, for example, polyoxy-40-stearate. In certain embodiments, the active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are made by dissolving or dispensing the compound in the proper medium. As discussed above, penetration enhancing agents can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0219] It will also be appreciated that the compounds and pharmaceutical compositions of the present invention can be formulated and employed in combination therapies, that is, the compounds and pharmaceutical compositions can be formulated with or administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another anticancer agent), or they may achieve different effects (*e.g.*, control of any adverse effects).

[0220] For example, other therapies or therapeutic agents that may be used in combination with the inventive compounds of the present invention include surgery, radiotherapy (in but a few examples, γ-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), to name a few. For a more comprehensive discussion of updated cancer therapies see, The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference. See also the National Cancer Institute (CNI) website (www.nci.nih.gov) and the Food and Drug Administration (FDA) website for a list of the FDA approved oncology drugs (www.fda.gov/cder/cancer/druglistframe – See Appendix A).

[0221] In certain embodiments, the pharmaceutical compositions of the present invention further comprise one or more additional therapeutically active ingredients (*e.g.*,

chemotherapeutic and/or palliative). For purposes of the invention, the term *"Palliative"* refers to treatment that is focused on the relief of symptoms of a disease and/or side effects of a therapeutic regimen, but is not curative. For example, palliative treatment encompasses painkillers, antinausea medications and anti-sickness drugs. In addition, chemotherapy, radiotherapy and surgery can all be used palliatively (that is, to reduce symptoms without going for cure; *e.g.*, for shrinking tumors and reducing pressure, bleeding, pain and other symptoms of cancer).

[0222] **4) Research Uses, Pharmaceutical Uses and Methods of Treatment**

[0223] *Research Uses*

[0224] According to the present invention, the inventive compounds may be assayed in any of the available assays known in the art for identifying compounds having antiangiogenic activity and/or antiproliferative activity. For example, the assay may be cellular or non-cellular, *in vivo* or *in vitro*, high- or low-throughput format, etc.

[0225] Thus, in one aspect, compounds of this invention which are of particular interest include those which:

- exhibit activity as inhibitors of cell migration;
- exhibit an antiproliferative and/or an antiangiogenic effect on solid tumors; and/or
- exhibit a favorable therapeutic profile (*e.g.*, safety, efficacy, and stability).

[0226] As discussed above, certain of the compounds as described herein exhibit activity generally as inhibitors of cell migration and/or angiogenesis. More specifically, compounds of the invention act as inhibitors of tumor growth and angiogenesis.

[0227] As detailed in the exemplification herein, in assays to determine the ability of compounds to inhibit tumor cell migration (*e.g.*, wound healing assay), certain inventive compounds exhibited IC_{50} values $\leq$ 50 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 40 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 30 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 20 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 10 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 7.5 μM. In certain embodiments,

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inventive compounds exhibit IC_{50} values $\leq$ 5 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 2.5 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 1 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.75 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.5 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.25 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.1 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 750 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 500 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 250 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 100 nM. In other embodiments, exemplary compounds exhibited IC_{50} values $\leq$ 75 nM. In other embodiments, exemplary compounds exhibited IC_{50} values $\leq$ 50 nM.

[0228] As detailed in the exemplification herein, in assays to determine the ability of compounds to inhibit tumor cell proliferation, certain inventive compounds exhibited IC_{50} values $\leq$ 200 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 150 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 100 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 50 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 10 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 7.5 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 5 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 2.5 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 1 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.75 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.5 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.25 μM. In certain embodiments, inventive compounds exhibit IC_{50} values $\leq$ 0.1 μM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 750 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 500 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 250 nM. In certain other embodiments, inventive compounds exhibit IC_{50} values $\leq$ 100 nM. In other embodiments, exemplary compounds exhibited IC_{50} values $\leq$ 75 nM. In other embodiments, exemplary compounds exhibited IC_{50} values $\leq$ 50 nM.

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[0229] In certain embodiments, the present invention provides methods for identifying Migrastatin analogs useful in the preparation of pharmaceutical compositions for the treatment of various disorders including cancer, metastasis and disorders involving increased angiogenesis.

[0230] In certain exemplary embodiments, there is provided a method for identifying Migrastatin analogs having anti-angiogenic activity, the method comprising steps of:

a. adding a volume (e.g., 150μL) of matrigel into a plurality of reaction vessels;

b. effecting gelatinization of the matrigel for 30 minutes at 37°C;

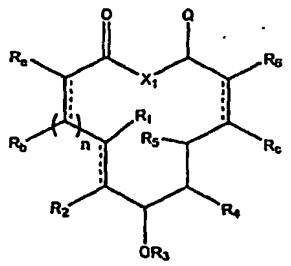
c. treating an 80-90% confluent HUVEC cell cultre with trypsin;

d. detaching the cells and collecting them by a collecting means (e.g., centrifugation);

e. adjusting the cell concentration to 100.000 cells.mL;

f. introducing a volume (e.g., 400 μL) of cell suspension in each of the reaction vessels;

g. adding in each of the reaction vessels a volume of a test solution comprising a test compound at a concentration ≤ 200μM, said compound having the structure:



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wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is

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independently -O-, -S- or -NR^{1C}-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{6A}$, -NO_2, -COR^{6A}, -CO_2R^{6A}, -$NR^{6A}C(=O)R^{6B}$, -$NR^{6A}C(=O)OR^{6B}$, -$CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{6A}; wherein W is independently -O-, -S- or -NR^{6C}-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, -$S(O)_{1-2}R^{a1}$, -NO_2, -COR^{a1}, -CO_2R^{a1}, -$NR^{a1}C(=O)R^{a2}$, -$NR^{a1}C(=O)OR^{a2}$, -$CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{a1}; wherein W is independently -O-, -S- or -NR^{a3}-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, -$S(O)_{1-2}R^{c1}$, -NO_2, -COR^{c1}, -CO_2R^{c1}, -$NR^{c1}C(=O)R^{c2}$, -$NR^{c1}C(=O)OR^{c2}$, -$CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or –WR^{c1}; wherein W is independently -O-, -S- or -NR^{c3}-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

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n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and
pharmaceutically acceptable derivatives thereof;

h. incubating the cells at 37°C with 5% CO_2 for 16-18 hours;

i. removing the media from each reaction vessel and washing with an appropriate solvent (e.g., 2×500μL PBS);

j. adding a volume of 8μM Calcein AM in PBS;

k. incubating the cells for 30 minutes at 37°C;

l. washing with an appropriate solvent (e.g., 2×500μL PBS);

m. visualizing the cells under an inverted microscope (fluorescence excited at 488 nm and recorded at 538 nm); and

n. comparing the disturbance of the complexity of the tube network with that observed for cells exposed to 100μM Migrastatin.

[0231] In certain embodiments, the method is for identifying Migrastatin analogs useful in the preparation of pharmaceutical compositions for the treatment of angiogenesis-related disorders

[0232] In certain embodiments, in step g above, a different concentration of the same test compound is introduced in each reaction vessel. In certain other embodiments, a different test

compound is introduced in each reaction vessel. In certain embodiments, in step g above, a different concentration of the same test compound is introduced in a subset of the reaction vessels; and a different test compound is introduced in another subset of the reaction vessels.

[0233] According to the present invention, the method is preferably practiced with dense arrays of reaction vessels. Preferably, the center-to-center distance between reaction vessels is less than about 8.5 mm. More preferably, the distance is less than 4.5 mm. Even more preferably the distance is less than approximately 2.25 mm. Most preferably, the distance is less than approximately 1 mm. In certain embodiments, the method is performed with a 48-well culture dish.

[0234] Conventional high throughput screens are often performed in commercially available 48- or 96-well plates (see, for example, Rice et al. *Anal. Biochem.* 241:254-259. 1996). Such plates may be utilized according to the present invention. However, denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 48- or 96-well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL; Corning Costar, Corning, NY) or 1536 (Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. The inventive method is compatible with any or all of these array formats.

[0235] In certain exemplary embodiments, there is provided a method for identifying Migrastatin analogs having cell migration inhibitory activity, the method comprising steps of:

a. growing adherent cancer cells to confluence in a suitable media (*e.g.* KYSE-520 cells in RPMI-1640 with 10 % FBS);

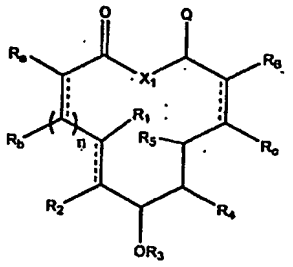
b. starving said cells for 24 h in serum free media;

c. applying a scratch (ca. 0.5 mm) to the cell layer surface;

d. removing said media;

e. washing said cells with a suitable solution (*e.g.*, PBS);

f. adding serum free media comprising a test compound at a concentration ≤ 200μM, said compound having the structure:



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wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic,

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alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and
pharmaceutically acceptable derivatives thereof;

g. incubating the cells for 28 to 30 h at 37 °C, 5 % CO_2; and

h. comparing the wound healing effect with that observed for cells exposed to 100μM Migrastatin.

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[0236] In certain embodiments, the method is for identifying Migrastatin analogs useful in the preparation of pharmaceutical compositions for the treatment of metastasis-related disorders

[0237] In certain embodiments, the method may be adapted to high-throughput format wherein the cells and test compounds are introduced and assayed in each of a plurality of reaction vessels.

[0238] In certain exemplary embodiments, there is provided a method for identifying Migrastatin analogs having cell migration inhibitory activity, the method comprising steps of:

a. growing cells to 70 to 80 % confluence in a suitable media;

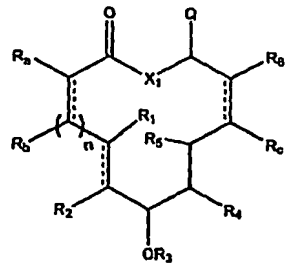
b. incubating said cells in serum and growth factor free media for 24 h;

c. detaching said cells by trypsin treatment, collecting the cells by centrifugation and resuspending them in serum free media to a final concentration of 150,000 cells/mL;

d. loading a volume (*e.g.*, 400 μL) of the cell suspension into a fibronectin coated insert for 24 well multidishes;

e. applying a volume (*e.g.*, 750 μL) of fully supplemented media to the compartment under said insert;

f. adding to both the insert and the compartment a solution comprising a test compound at a concentration ≤ 200μM, said compound having the structure:



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wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$, $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or

heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5;

$\mathbf{X_1}$ is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and
pharmaceutically acceptable derivatives thereof;

g. incubating the cells for 36 h at 37 °C, 5 % CO_2;

h. aspirating the media from both the insert and the lower compartment;

i. filling the lower compartment with a volume (*e.g.*, 300 µL) of CyQuant assay solution (Molecular Probes, Eugene, OR);

j. incubating at room temperature for 5min;

k. recording the fluorescence signal in an appropriate reader; and

l. determining the cell migration inhibitory effect of the test compound.

[0239] In certain embodiments, the method is for identifying Migrastatin analogs useful in the preparation of pharmaceutical compositions for the treatment of metastasis-related disorders

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[0240] *Pharmaceutical Uses and Methods of Treatment*

[0241] In yet another aspect, the present invention provides methods of treatment of various disorders, including those associated with metastasis and/or increased angiogenic activity. In certain embodiments, according to the methods of treatment of the present invention, metastasis and/or the growth of tumor cells is inhibited by contacting said tumor cells with an inventive compound or composition, as described herein.

[0242] Accordingly, in another aspect of the invention, methods for the treatment of cancer are provided comprising administering a therapeutically effective amount of a compound of formula (I), as described herein, to a subject in need thereof. In certain embodiments, a method for the treatment of cancer is provided comprising administering a therapeutically effective amount of an inventive compound, or a pharmaceutical composition comprising an inventive compound to a subject in need thereof, in such amounts and for such time as is necessary to achieve the desired result.

[0243] In certain embodiments, the method involves the administration of a therapeutically effective amount of the compound or a pharmaceutically acceptable derivative thereof to a subject (including, but not limited to a human or animal) in need of it. In certain embodiments, the inventive compounds as useful for the treatment of cancer (including, but not limited to, glioblastoma, retinoblastoma, breast cancer, cervical cancer, colon and rectal cancer, leukemia, lymphoma, lung cancer (including, but not limited to small cell lung cancer), melanoma and/or skin cancer, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer and gastric cancer, bladder cancer, uterine cancer, kidney cancer, testicular cancer, stomach cancer, brain cancer, liver cancer, or esophageal cancer).

[0244] As discussed above, the compounds of the present invention are inhibit metastasis of tumor cells and/or inhibiting the growth of tumor cells. In general, the inventive anticancer agents are useful in the treatment of cancers and other proliferative disorders, including, but not limited to breast cancer, cervical cancer, colon and rectal cancer, leukemia, lung cancer, melanoma, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, and gastric cancer, to name a few. In certain embodiments, the inventive anticancer agents are active against leukemia cells and melanoma cells, and thus are useful for

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the treatment of leukemias (*e.g.*, myeloid, lymphocytic, myelocytic and lymphoblastic leukemias) and malignant melanomas. In still other embodiments, the inventive anticancer agents are active against solid tumors.

[0245] In certain embodiments, the present invention provides a method for preventing metastasis of tumor cells in a subject comprising administering to a subject (including, but not limited to, a human or animal) in need thereof a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. In certain exemplary embodiments, the method is used to prevent metastasis of prostate, breast, colon, bladder, cervical, skin, testicular, kidney, ovarian, stomach, brain, liver, pancreatic or esophageal cancer or lymphoma, leukemia, or multiple myeloma, to name a few.

[0246] In another aspect, the present invention provides methods for decreasing migration of tumor cells. In a further aspect, the present invention provides methods for decreasing anchorage-independent growth of tumor cells. In yet a further aspect, the present invention provides methods for inhibiting angiogenesis.

[0247] In yet another aspect, the present invention provides methods for preventing unwanted angiogenesis in a subject (including, but not limited to, a human or animal).

[0248] As used herein, the term "angiogenesis" means the generation of new blood vessels into a tissue or organ. Under normal physiological conditions, humans or animals only undergo angiogenesis in very specific restricted situations. For example, angiogenesis is normally observed in wound healing, fetal and embryonal development and formation of the corpus luteum, endometrium and placenta. The control of angiogenesis is a highly regulated system of angiogenic stimulators and inhibitors. The control of angiogenesis has been found to be altered in certain disease states and, in many cases, the pathological damage associated with the disease is related to the uncontrolled angiogenesis.

[0249] Both controlled and uncontrolled angiogenesis are thought to proceed in a similar manner. Endothelial cells and pericytes, surrounded by a basement membrane, form capillary blood vessels. Angiogenesis begins with the erosion of the basement membrane by enzymes released by endothelial cells and leukocytes. The endothelial cells, which line the lumen of blood vessels, then protrude through the basement membrane. Angiogenic stimulants induce the endothelial cells to migrate through the eroded basement membrane. The migrating cells form a

"sprout" off the parent blood vessel, where the endothelial cells undergo mitosis and proliferate. The endothelial sprouts merge with each other to form capillary loops, creating the new blood vessel. In the disease state, prevention of angiogenesis could avert the damage caused by the invasion of the new microvascular system.

[0250] Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due to unregulated angiogenesis have been grouped together as angiogenic dependent or angiogenic associated diseases. Therapies directed at control of the angiogenic processes could lead to the abrogation or mitigation of these diseases.

[0251] One example of a disease involving an angiogenic process is ocular neovascular disease. This disease is characterized by invasion of new blood vessels into the structures of the eye such as the retina or cornea. It is the most common cause of blindness and is involved in approximately twenty eye diseases. In age-related macular degeneration, the associated visual problems are caused by an ingrowth of chorioidal capillaries through defects in Bruch's membrane with proliferation of fibrovascular tissue beneath the retinal pigment epithelium. Angiogenic damage is also associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia. Other diseases associated with corneal neovascularization include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections, Kaposi's sarcoma, Mooren's ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, pemphigoid, radial keratotomy, and corneal graph rejection.

[0252] Diseases associated with retinal/choroidal neovascularization include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus

erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy.

[0253] Another disease in which angiogenesis is believed to be involved is rheumatoid arthritis. The blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis.

[0254] Factors associated with angiogenesis may also have a role in osteoarthritis. The activation of the chondrocytes by angiogenic-related factors contributes to the destruction of the joint. At a later stage, the angiogenic factors would promote new bone formation. Therapeutic intervention that prevents the bone destruction could halt the progress of the disease and provide relief for persons suffering with arthritis.

[0255] Chronic inflammation may also involve pathological angiogenesis. Such disease states as ulcerative colitis and Crohn's disease show histological changes with the ingrowth of new blood vessels into the inflamed tissues. Bartonellosis, a bacterial infection found in South America, can result in a chronic stage that is characterized by proliferation of vascular endothelial cells. Another pathological role associated with angiogenesis is found in atherosclerosis. The plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity.

[0256] One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate. Therapy-resistant hemangiomas exist that cannot be treated with therapeutics currently in use.

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[0257] Angiogenesis is also responsible for damage found in hereditary diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, tumors of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal bleeding and sometimes with pulmonary or hepatic arteriovenous fistula.

[0258] Angiogenesis is prominent in solid tumor formation and metastasis. Angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. A tumor cannot expand without a blood supply to provide nutrients and remove cellular wastes. Tumors in which angiogenesis is important include solid tumors, and benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas. Prevention of angiogenesis could halt the growth of these tumors and the resultant damage to the animal due to the presence of the tumor.

[0259] It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors.

[0260] Angiogenesis is important in two stages of tumor metastasis. The first stage where angiogenesis stimulation is important is in the vascularization of the tumor which allows tumor cells to enter the blood stream and to circulate throughout the body. After the tumor cells have left the primary site, and have settled into the secondary, metastasis site, angiogenesis must occur before the new tumor can grow and expand. Therefore, prevention of angiogenesis could lead to the prevention of metastasis of tumors and possibly contain the neoplastic growth at the primary site.

[0261] Knowledge of the role of angiogenesis in the maintenance and metastasis of tumors has led to a prognostic indicator for breast cancer. The amount of neovascularization found in the primary tumor was determined by counting the microvessel density in the area of the most intense neovascularization in invasive breast carcinoma. A high level of microvessel

density was found to correlate with tumor recurrence. Control of angiogenesis by therapeutic means could possibly lead to cessation of the recurrence of the tumors.

[0262] Angiogenesis is also involved in normal physiological processes such as reproduction and wound healing. Angiogenesis is an important step in ovulation and also in implantation of the blastula after fertilization. Prevention of angiogenesis could be used to induce amenorrhea, to block ovulation or to prevent implantation by the blastula.

[0263] In wound healing, excessive repair or fibroplasia can be a detrimental side effect of surgical procedures and may be caused or exacerbated by angiogenesis. Adhesions are a frequent complication of surgery and lead to problems such as small bowel obstruction.

[0264] Accordingly, it is an object of the present invention to provide a method to inhibit unwanted angiogenesis in a subject (including, but not limited to, a human or animal).

[0265] It is another object of the present invention to provide a method for the treatment for diseases mediated by angiogenesis.

[0266] It is yet another object of the present invention to provide a method for the treatment for macular degeneration.

[0267] It is yet another object of the present invention to provide a method for the treatment for all forms of proliferative vitreoretinopathy including those forms not associated with diabetes.

[0268] It is yet another object of the present invention to provide a method for the treatment for solid tumors.

[0269] It is yet another object of the present invention to provide a method for the treatment of blood-borne tumors, such as leukemia.

[0270] It is another object of the present invention to provide a method for the treatment of hemangioma.

[0271] It is another object of the present invention to provide a method for the treatment of retrolental fibroplasia.

[0272] It is another object of the present invention to provide a method for the treatment of psoriasis.

[0273] It is another object of the present invention to provide a method for the treatment of Kaposi's sarcoma.

[0274] It is another object of the present invention to provide a method for the treatment of Crohn's disease.

[0275] It is another object of the present invention to provide a method for the treatment of diabetic retinopathy.

[0276] Thus, in certain embodiments, the invention provides a method for preventing unwanted angiogenesis in a subject (including, but not limited to, a human or animal) comprising administering to a subject in need thereof a therapeutically effective amount of the compound of the invention in an amount effective to inhibit angiogenesis.

[0277] In certain other embodiments, the invention provides a method for treating an angiogenesis-dependent disease in a subject (including, but not limited to, a human or animal) comprising administering to a subject in need thereof a therapeutically effective amount of the compound of the invention in an amount effective to inhibit angiogenesis.

[0278] Diseases associated with corneal neovascularization that can be treated according to the present invention include but are not limited to, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical bums, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections, Kaposi's sarcoma, Mooren's ulcer, Terrien's marginal degeneration, mariginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, pemphigoid, radial keratotomy, and corneal graph rejection.

[0279] Diseases associated with retinal/choroidal neovascularization that can be treated according to the present invention include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-

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laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes.

[0280] Diseases associated with chronic inflammation can be treated by the compositions and methods of the present invention. Diseases with symptoms of chronic inflammation include inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis and rheumatoid arthritis. Angiogenesis is a key element that these chronic inflammatory diseases have in common. The chronic inflammation depends on continuous formation of capillary sprouts to maintain an influx of inflammatory cells. The influx and presence of the inflammatory cells produce granulomas and thus, maintains the chronic inflammatory state. Inhibition of angiogenesis by the compositions and methods of the present invention would prevent the formation of the granulomas and alleviate the disease.

[0281] The compositions and methods of the present invention can be used to treat patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Both Crohn's disease and ulcerative colitis are characterized by chronic inflammation and angiogenesis at various sites in the gastrointestinal tract. Crohn's disease is characterized by chronic granulomatous inflammation throughout the gastrointestinal tract consisting of new capillary sprouts surrounded by a cylinder of inflammatory cells. Prevention of angiogenesis by the compositions and methods of the present invention inhibits the formation of the sprouts and prevents the formation of granulomas.

[0282] Crohn's disease occurs as a chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may also occur in any part of the gastrointestinal tract from the mouth to the anus and perianal area. Patients with Crohn's disease generally have chronic diarrhea associated with abdominal pain, fever, anorexia, weight loss and abdominal swelling. Ulcerative colitis is also a chronic, nonspecific, inflammatory and ulcerative disease arising in the colonic mucosa and is characterized by the presence of bloody diarrhea.

[0283] The inflammatory bowel diseases also show extraintestinal manifestations such as skin lesions. Such lesions are characterized by inflammation and angiogenesis and can occur at many sites other than the gastrointestinal tract. The compositions and methods of the present

invention are also capable of treating these lesions by preventing the angiogenesis, thus reducing the influx of inflammatory cells and the lesion formation.

[0284] Sarcoidosis is another chronic inflammatory disease that is characterized as a multisystem granulomatous disorder. The granulomas of this disease may form anywhere in the body and thus the symptoms depend on the site of the granulomas and whether the disease active. The granulomas are created by the angiogenic capillary sprouts providing a constant supply of inflammatory cells.

[0285] The compositions and methods of the present invention can also treat the chronic inflammatory conditions associated with psoriasis. Psoriasis, a skin disease, is another chronic and recurrent disease that is characterized by papules and plaques of various sizes. Prevention of the formation of the new blood vessels necessary to maintain the characteristic lesions leads to relief from the symptoms.

[0286] Another disease which can be treated according to the present invention is rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disease characterized by nonspecific inflammation of the peripheral joints. It is believed that the blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis. Another disease that can be treated according to the present invention are hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, solid or blood borne tumors and acquired immune deficiency syndrome.

[0287] It will be appreciated that the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for the treatment of cancer and/or disorders associated with metastasis and/or angiogenesis. Thus, the expression "effective amount" as used herein, refers to a sufficient amount of agent to inhibit the growth of tumor cells, or refers to a sufficient amount to reduce the effects of cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the diseases, the particular anticancer agent, its mode of administration, and the like.

[0288] The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (see, for example, Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference in its entirety).

[0289] Furthermore, after formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, the pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, creams or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered at dosage levels of about 0.001 mg/kg to about 50 mg/kg, from about 0.01 mg/kg to about 25 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. It will also be appreciated that dosages smaller than 0.001 mg/kg or greater than 50 mg/kg (for example 50-100 mg/kg) can be administered to a subject. In certain embodiments, compounds are administered orally or parenterally.

TREATMENT KIT

[0290] In other embodiments, the present invention relates to a kit for conveniently and effectively carrying out the methods in accordance with the present invention. In general, the

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pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Alternatively, placebo dosages, or calcium dietary supplements, either in a form similar to or distinct from the dosages of the pharmaceutical compositions, can be included to provide a kit in which a dosage is taken every day. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

EQUIVALENTS

[0291] The representative examples that follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art. Throughput this document, various publications are referred to, each of which is hereby incorporated by reference in its entirety in an effort to more fully describe the state of the art to which the invention pertains.

[0292] The following examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

EXEMPLIFICATION

[0293] The compounds of this invention and their preparation can be understood further by the examples that illustrate some of the processes by which these compounds are prepared or used. It will be appreciated, however, that these examples do not limit the invention. Variations of the invention, now known or further developed, are considered to fall within the scope of the present invention as described herein and as hereinafter claimed.

[0294] ***1) General Description of Synthetic Methods:***

[0295] The practitioner has a a well-established literature of macrolide chemistry to draw upon, in combination with the information contained herein, for guidance on synthetic strategies, protecting groups, and other materials and methods useful for the synthesis of the compounds of this invention.

[0296] The various references cited herein provide helpful background information on preparing compounds similar to the inventive compounds described herein or relevant intermediates, as well as information on formulation, uses, and administration of such compounds which may be of interest.

[0297] Moreover, the practitioner is directed to the specific guidance and examples provided in this document relating to various exemplary compounds and intermediates thereof.

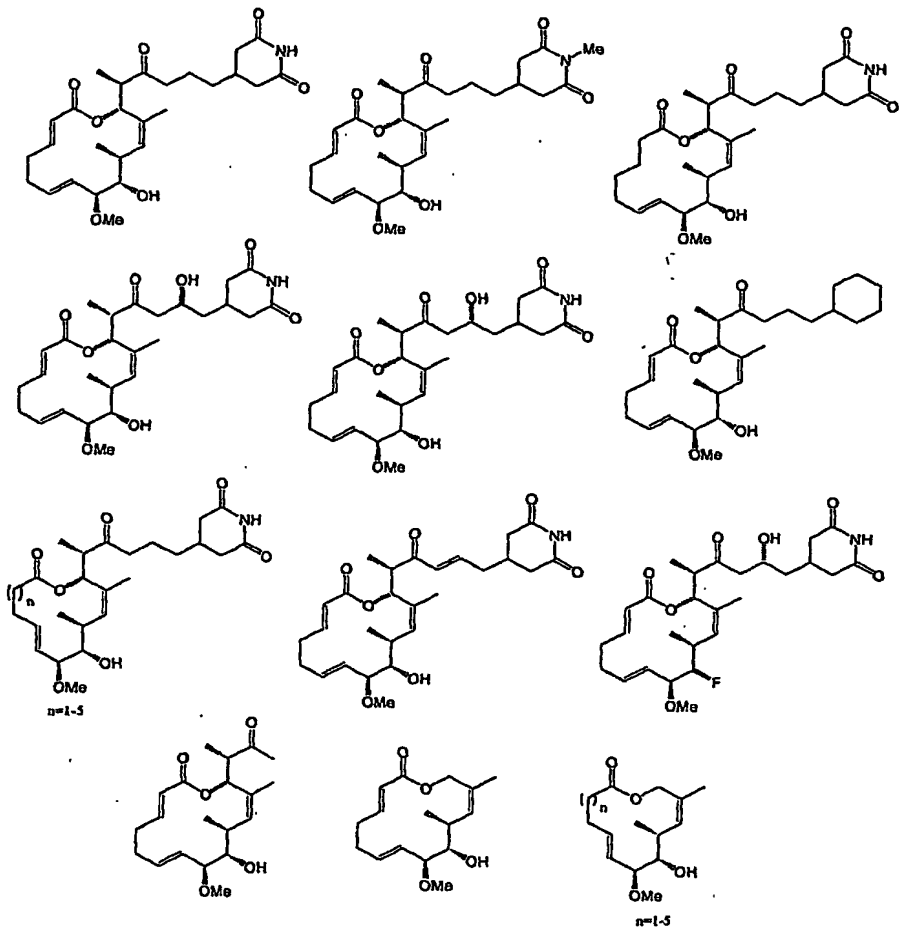
[0298] The compounds of this invention and their preparation can be understood further by the examples that illustrate some of the processes by which these compounds are prepared or used. It will be appreciated, however, that these examples do not limit the invention. Variations of the invention, now known or further developed, are considered to fall within the scope of the present invention as described herein and as hereinafter claimed.

[0299] According to the present invention, any available techniques can be used to make or prepare the inventive compounds or compositions including them. For example, a variety of solution phase synthetic methods such as those discussed in detail below may be used. Alternatively or additionally, the inventive compounds may be prepared using any of a variety combinatorial techniques, parallel synthesis and/or solid phase synthetic methods known in the art.

[0300] It will be appreciated as described below, that a variety of inventive compounds can be synthesized according to the methods described herein. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or are prepared by methods well known to a person of ordinary skill in the art following procedures described in such references as Fieser and Fieser 1991, "Reagents for Organic Synthesis", vols 1-17, John Wiley and Sons, New York, NY, 1991; Rodd 1989 "Chemistry of Carbon Compounds", vols. 1-5 and supps, Elsevier Science Publishers, 1989; "Organic Reactions", vols 1-40, John Wiley and Sons, New York, NY, 1991; March 2001, "Advanced Organic Chemistry", 5th ed. John Wiley and Sons, New York, NY; and Larock 1990, "Comprehensive Organic Transformations: A Guide to Functional Group Preparations", 2nd ed. VCH Publishers. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to a person of ordinary skill in the art having regard to this disclosure.

[0301] The starting materials, intermediates, and compounds of this invention may be isolated and purified using conventional techniques, including filtration, distillation, crystallization, chromatography, and the like. They may be characterized using conventional methods, including physical constants and spectral data.

[0302] Certain exemplary compounds of the invention are listed below:



[0303] **General Reaction Procedures:**

[0304] Unless mentioned specifically, reaction mixtures were stirred using a magnetically driven stirrer bar. An inert atmosphere refers to either dry argon or dry nitrogen. Reactions were monitored either by thin layer chromatography, by proton nuclear magnetic resonance (NMR) or by high-pressure liquid chromatography (HPLC), of a suitably worked up sample of the reaction mixture.

[0305] Listed below are abbreviations used for some common organic reagents referred to herein:

[0306] CSA: Camphorsulphonic acid

[0307] DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

[0308] Dess-Martin: Dess-Martin periodinane

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[0309]	DIBAL-H:	Diisobutyl aluminum hydride
[0310]	DMAP:	*N,N*-Dimethylaminopyridine
[0311]	DMF:	*N,N*-Dimethylformamide
[0312]	TBSOTf:	*Tert* -butyl- dimethylsilyl triflate
[0313]	TESCl:	Triethylsilyl chloride
[0314]	TFA:	Trifluoroacetic acid
[0315]	TMSCl:	Trimethylsilyl chloride
[0316]	THF:	Tetrahydrofuran

[0317] **General Work Up Procedures:**

[0318] Unless mentioned specifically, reaction mixtures were cooled to room temperature or below then quenched, when necessary, with either water or a saturated aqueous solution of ammonium chloride. Desired products were extracted by partitioning between water and a suitable water-immiscible solvent (*e.g.* ethyl acetate, dichloromethane, diethyl ether). The desired product containing extracts were washed appropriately with water followed by a saturated solution of brine. On occasions where the product containing extract was deemed to contain residual oxidants, the extract was washed with a 10% solution of sodium sulphite in saturated aqueous sodium bicarbonate solution, prior to the aforementioned washing procedure. On occasions where the product containing extract was deemed to contain residual acids, the extract was washed with saturated aqueous sodium bicarbonate solution, prior to the aforementioned washing procedure (except in those cases where the desired product itself had acidic character). On occasions where the product containing extract was deemed to contain residual bases, the extract was washed with 10% aqueous citric acid solution, prior to the aforementioned washing procedure (except in those cases where the desired product itself had basic character). Post washing, the desired product containing extracts were dried over anhydrous magnesium sulphate, and then filtered. The crude products were then isolated by removal of solvent(s) by rotary evaporation under reduced pressure, at an appropriate temperature (generally less than 45°C).

[0319] **General Purification Procedures:**

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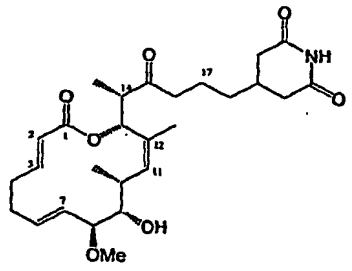
[0320] Unless mentioned specifically, chromatographic purification refers to flash column chromatography on silica, using a single solvent or mixed solvent as eluent. Suitably purified desired product containing elutes were combined and concentrated under reduced pressure at an appropriate temperature (generally less than 45°C) to constant mass. Final compounds were dissolved in 50% aqueous acetonitrile, filtered and transferred to vials, then freeze-dried under high vacuum before submission for biological testing.

[0321] Analytical Equipment:

[0322] Optical rotations were measured on a JASCO DIP-370 digital polarimeter at rt. Concentration (*c*) in g/100 ml and solvent are given in parentheses. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AMX-400 MHz or a Bruker Advance DRX-500 MHz spectrometer in $CDCl_3$ (referenced to 7.26 ppm (δ) for ^{1}H-NMR and 77.0 ppm for ^{13}C-NMR). Coupling constants (*J*) (H,H) are given in Hz, spectral splitting patterns are designated as singulet (s), doublet (d), triplet (t), quadruplet (q), multiplet or more overlapping signals (m), apparent (app), broad signal (br). Low resolution mass spectra (ionspray, a variation of electrospray) were acquired on a Perkin-Elmer Sciex API 100 spectrometer. Samples were introduced by direct infusion. High resolution mass spectra (fast atom bombardment, FAB) were acquired on a Micromass 70-SE-4F spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer as a film in $CHCl_3$ (NaCl plates). Absorption bands are noted in cm^{-1}.

[0323] **Example 1: Preparation of Migrastatin (1)**



(1)

[0324] Step 1: Preparation of Compound 3:

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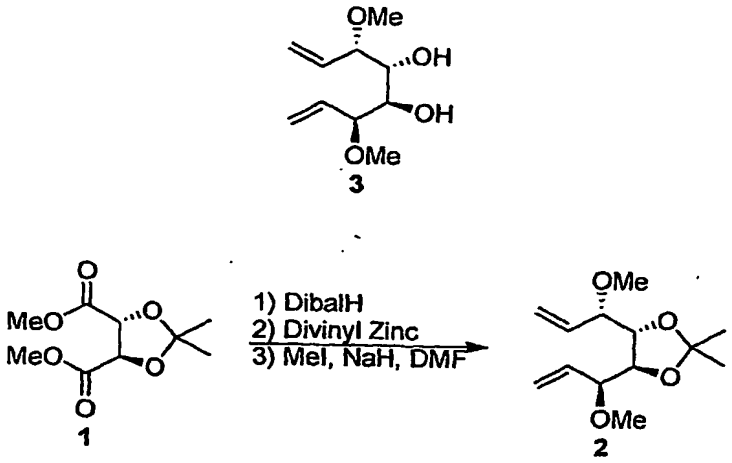

[0325] Conditions reported by Madsen (for zinc addition: Jorgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630) and Chang were used (for methylation and deprotection: Lee, W. W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473) starting from commercially available (Aldrich) **1**.

[0326] Commercially available Dimethyl 2,3-*O*-isopropylidene-L-tartrate (**1**, 14.42mL, 78.6mmol, 1 equiv) was dissolved in toluene (200mL) and cooled to –78°C before addition of DIBALH (180mL, 180mmol, 2.3 equiv). The reaction is allowed to stir for 3 hours before the addition of vinyl-zinc (prepared from Vinyl-Grignard (1.0M in THF) 588mL, 588mmol, 7.4 equiv and $ZnCl_2$ 40g, 294mmol, 3.7 equiv). The reaction was allowed to stir at –78°C for 1 hour at which point the cooling bath was removed the stirring continued for another 3 hours before quenching with saturated ammonium chloride and 20% Na/K-tartrate solution and extracting 4 times with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated to give a crude oil which was used directly for the next step. The crude oil was dissolved in dry DMF (300mL) and cooled to 0C before careful addition of NaH (6920mg, 157.2 mmol, 2.2 equiv). After stirring for 10 minutes MeI (11.7g, 188.6 mmol, 2.4 equiv) was added, the cooling bath removed and stirring continued overnight. The reaction mixture was quenched by the addition of ammonium hydroxide and aqueous layer was extracted five times with ether. The combined organic layers were washed five times with water, dried over Na_2SO_4 and evaporated.

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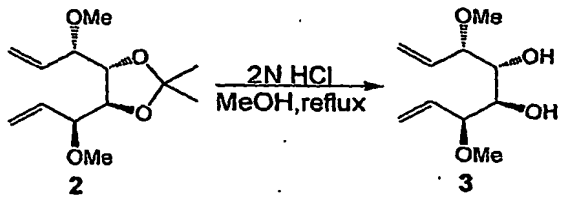
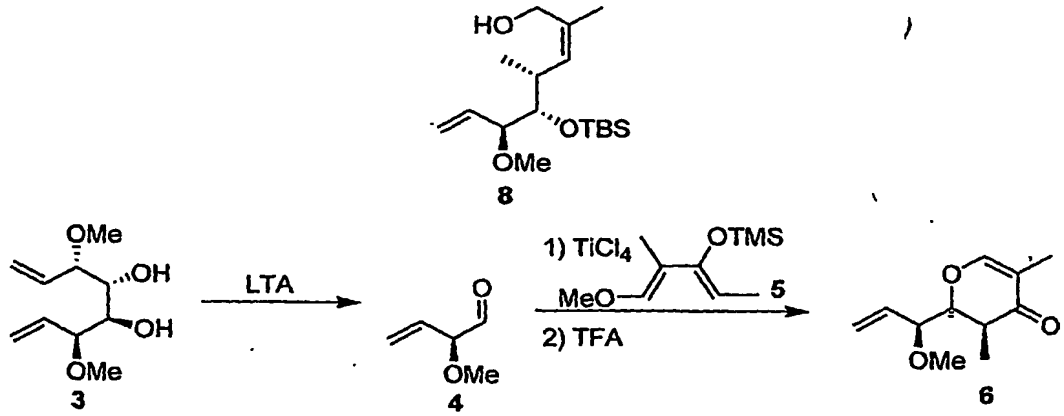


2 3

[0327] The crude oil thus obtained above was dissolved in MeOH (200 mL) and 2N HCl (200 mL) and refluxed for 1 hour. Following cooling of the reaction mixture, solid Na2CO3 was added to neutralize. The resulting slurry was filtered, evaporated (MeOH) and taken up in ethyl acetate and brine. The aqueous phase was extracted four times and the combined extracts were dried over Na_2SO_4, filtered and evaporated. The crude oil was chromatographed over a column of silica gel (gradient elution, 20-30% EtOAc/Hexanes) to give 3 as a clear yellow oil (12g, 59.3 mmol, 75% yield over 3 steps).

[0328] **Compound 3**: $[\alpha]_D$ +31.0° (*c* 1.77, $CHCl_3$); IR (neat) 3454, 3078, 2982, 2936, 2824, 1643, 1420, 1192, 1102, 992, 973, 925; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.77-5.71 (m, 2H), 5.36-5.32 (m, 4H), 3.81 (app t, J = 6.3, 2H), 3.76 (d, J = 5.5, 2H), 3.32 (s, 6H), 2.96 (br s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.08, 119.27, 86.65, 71.23, 57.15; MS (ESI) 225 [M+Na^+]; HRMS (FAB) calcd. for $C_{10}H_{18}O_4Na$ [M+Na^+] 225.1103, found 225.1079.

[0329] Step 2: Preparation of Compound 8:



[0330] To a strirred solution of 3 (455mg, 2.25 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at OC was added Na_2CO_3 (250mg, 2.36 mmol, 1.05 equiv) followed by $Pb(OAc)_4$ (1.05g, 2.36 mmol, 1.05 equiv). The cooling bath was removed and stirring continued for 45 minutes, at which point 70μL of ethylene glycol were added and stirring continued for 3 more minutes. The reaction

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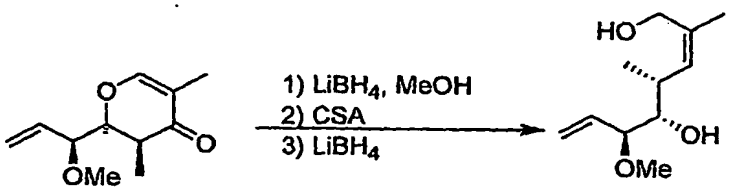
mixture was filtered through a Celite pad and the filtrate was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. This CH_2Cl_2 solution of **4** was transferred into a dry flame dried round bottom flask and cooled to –78C. To this stirred solution was added $TiCl_4$ (544 µL, 4.95 mmol, 1.1 equiv) followed 3 minutes later by **5** (1.08g, 5.4 mmol, 1.2 equiv). The reaction mixture was quenched 25 minutes later by the addition of MeOH and saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted 3 times with ether. The combined organic layers were dried over $MgSO_4$, evaporated, dissolved in CH_2Cl_2 and treated with TFA (2.5 mL). The crude reaction mixture was stirred with TFA for 75 minutes, then diluted with toluene (5 mL) and concentrated. This resulting crude oil was chromatographed over a column of silica gel (gradient elution, 6-12% EtOAc/Hexanes) to afford **6** as a clear oil (659 mg, 3.36 mmol, 75% yield over 3 steps).

[0331] **Compound 6**: $[\alpha]_D$ +77.1° (*c* 2.00, $CHCl_3$); IR (neat) 2980, 2938, 2883, 2827, 1785, 1671, 1622, 1602, 1460, 1387, 1305, 1214, 1176, 1085, 1010, 924, 697; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 5.63-5.54 (m, 1H), 5.48-5.43 (m, 2H), 4.25 (dd, J = 8.6, 2.9, 1H), 3.88 (app t, J = 8.5, 1H), 3.37 (s, 3H), 2.44 (dq, J = 7.2, 2.9, 1H), 1.68 (s, 3H), 1.07 (d, J = 7.2, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.99, 160.75, 131.79, 122.06, 112.51, 82.69, 81.99, 56.37, 40.62, 10.42, 9.96; MS (ESI) 219 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{11}H_{16}O_3Na$ [M+Na$^+$] 219.0997, found 219.0991.



6 **7**

[0332] To a stirred solution of pyrone **6** (2.51g, 12.8 mmol, 1.0 equiv) at 0°C in THF (21 mL) was added MeOH (622 µL, 15.36 mmol, 1.2 equiv) followed by $LiBH_4$ (2M in THF, 7.68 mL, 15.36 mmol, 1.2 equiv). After stirring for 10 minutes 0.2N HCl (20 mL) was added and stirring continued for 25 more minutes. The reaction mixture was diluted with EtOAc, the layers separated and the aqueous phase extracted further with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated. This crude oil was dissolved in THF (40 mL) and water (4 mL), treated with CSA (594 mg, 2.56 mmol, 0.2 equiv) and refluxed for 45 minutes. The reaction mixture was cooled to room temperature, quenched with saturated $NaHCO_3$, and

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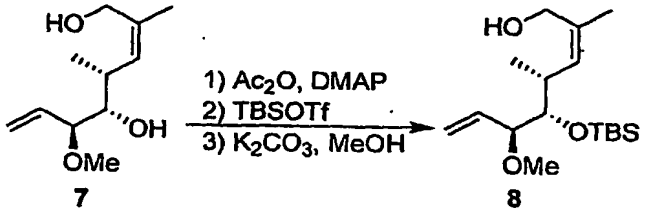
extracted 3 times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated. This crude oil was dissolved in THF (40 mL) and water (10 mL) and treated with $LiBH_4$ (2M in THF, 7.68 mL, 15.36 mmol, 1.2 equiv). The reaction mixture was stirred for 5 minutes at room temperature, quenched by the addition of 0.2N HCl (20 mL) and stirred for one more hour. This crude mixture was extracted 3 times with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and evaporated. The crude mixture chromatographed over a column of silica gel (gradient elution, 20-33% EtOAc/Hexanes) to afford diol **7** (1.34g, 6.7 mmol, 52% yield over 3 steps) as a clear oil.



7 **8**

[0333] To a stirred solution of diol **7** (446 mg, 2.23 mmol, 1.0 equiv) in CH_2Cl_2 10 mL) was added consecutively pyridine (270 μL, 3.34 mmol, 1.5 equiv), DMAP (cat), and Ac_2O (210 μL, 2.23 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 45 minutes, quenched by addition of saturated $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. This crude oil was dissolved in dry CH_2Cl_2 (15 mL) and treated with 2,6-lutidine (519 μL, 4.46 mmol, 2.0 equiv) and TBSOTf (767 μL, 3.34 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 25 minutes, quenched by addition of saturated $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The resulting crude oil was dissolved in MeOH (20 mL) and water (1.5 mL) and stirred with K_2CO_3 (1.54g, 11.14 mmol, 5equiv) for 2 hours at room temperature. The reaction mixture was quenched by addition of saturated $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, evaporated and the resulting oil chromatographed over a column of silica gel (gradient elution, 9-14% EtOAc/Hexanes) to afford alcohol **8** (536 mg, 1.7 mmol, 76% yield over 3 steps) as a clear oil.

[0334] **Compound 8**: $[\alpha]_D$ +3.8° (*c* 1.85, $CHCl_3$); IR (neat) 3352, 2957, 2930, 2857, 1472, 1462, 1250, 1127, 1081, 1028, 1006, 929, 834, 776; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.73-

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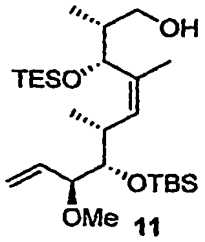
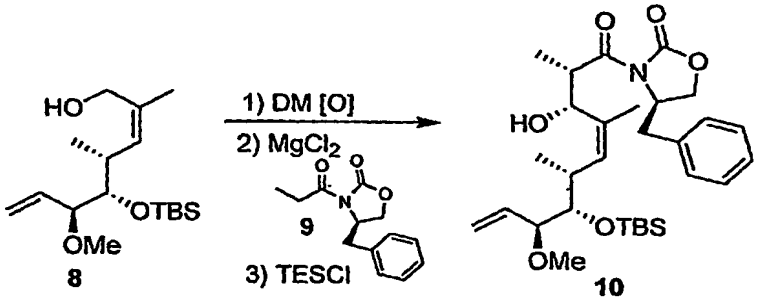
5.66 (m, 1H), 5.30-5.24 (m, 3H), 4.12 (dd, J = 11.8, 4.9, 1H), 4.00 (dd, J = 11.7, 6.5, 1H), 3.48-3.43 (m, 2H), 3.22 (s, 3H), 2.69-2.61 (m, 1H), 1.78 (d, J = 1.1, 3H), 1.68-1.66 (m, 1H), 0.91 (s, 12H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.15, 133.05, 118.54, 85.89, 78.28, 61.76, 56.12, 34.23, 26.11, 25.64, 21.53, 18.49, 15.32, –3.88, –4.70; MS (ESI) 337 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{17}H_{34}O_3NaSi$ [M+Na$^+$] 337.2175, found 337.2162.

[0335] Step 3: Preparation of Compound 11:



11



[0336] To a stirred solution of **8** (415 mg, 1.32 mmol, 1.0 equiv) in CH_2Cl_2 was added Dess-Martin periodinane (840 mg, 1.98 mmol, 1.5 equiv). After stirring at room temperature for 90 minutes the reaction was quenced with a 1:1 mixture of saturated sodium thiosulfate and saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted two more times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude mixture was dissolved in EtOAc (4 mL) along with **9** (461 mg, 1.98 mmol, 1.5 equiv), and was treated consecutively with Et_3N (460 µL, 3.30 mmol, 2.5 equiv), TMSCl (335 µL, 2.64 mmol, 2.0 equiv) and $MgCl_2$ (126 mg, 1.32 mmol, 1.0 equiv). The reaction mixture was stirred for 48 hours at room temperature, at which point it was filtered through a silica plug with ether and concentrated. The crude mixture was dissolved in MeOH (10 mL) and treated with 2 drops of TFA. After 15 minutes toluene (20 mL) was added and the mixture concentrated. The resulting oil was chromatographed over a column of silica gel employing 1:1 CH_2Cl_2/Hexanes as

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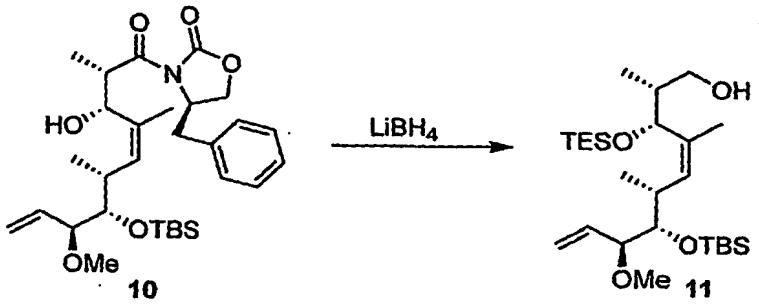
the eluent to yield the corresponding alcohol as a clear oil. The alcohol was dissolved in dry CH_2Cl_2 (13 mL) and treated with TESCl (440 μL, 2.64 mmol, 2 equiv) and imidazole (270 mg, 3.96 mmol, 3 equiv). The mixture was allowed to stir overnight at room temperature. This solution was then quenched by the addition of water, extracted 3 times with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was then chromatographed over a column of silica gel (gradient elution, 5-15% EtOAc/Hexanes) to afford TES-ether **10** (445 mg, 0.67 mmol, 51% yield over 3 steps) as a clear oil.



10 **11**

[0337] To a stirred solution of **10** (91 mg, 0.138 mmol, 1.0 equiv) in THF (4 mL) was added MeOH (23 μL, 0.551 mmol, 4 equiv) followed by $LiBH_4$ (12 mg, 0.551 mmol, 4 equiv). This reaction mixture was stirred at room temperature for 1 hour before being quenched by the addition of 0.5N NaOH. This mixture was extracted 3 times with ether, dried over $MgSO_4$ and evaporated to dryness. The crude was then chromatographed over a column of silica gel employing 10% EtOAc/Hexanes as the eluent to afford alcohol **11** (58 mg, 0.119 mmol, 86% yield).

[0338] **Compound 11**: $[\alpha]_D$ +10.9° (*c* 2.38, $CHCl_3$); IR (neat) 3460, 2970, 2930, 2880, 1460, 1380, 1250, 1130, 1060, 1020, 840, 740; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.60-5.53 (m, 1H), 5.35-5.26 (m, 3H), 4.31 (d, J = 9.1, 1H), 3.68-3.60 (m, 2H), 3.42-3.34 (m, 2H), 3.20 (s, 3H), 3.13 (app d, J = 7.0, 1H), 2.63-2.60 (m, 1H), 1.94-1.90 (m, 1H), 1.67 (d, J = 1.2, 3H), 0.94 (t, J = 8.1, 9H), 0.91 (m, 12H), 0.70 (d, J = 7.1, 3H), 0.58 (q, J = 8.0, 6H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.10, 133.66, 133.46, 118.84, 86.46, 78.30, 76.58, 68.33, 56.08, 38.87, 33.24, 26.13, 18.58, 17.70, 14.25, 12.64, 6.75, 4.74, –3.85, –4.89; MS (ESI) 509 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{26}H_{54}O_4NaSi_2$ [M+Na$^+$] 509.3458, found 509.3468.

[0339] <u>Step 4: Preparation of Compound 14</u>:

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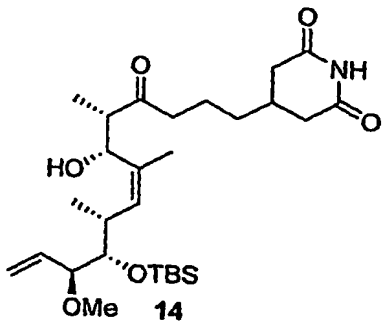

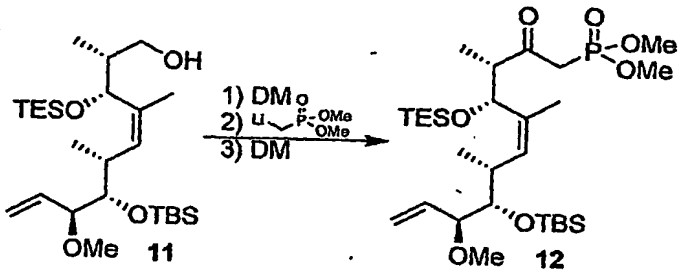

[0340] To a stirred solution of **11** (142 mg, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 was added Dess-Martin periodinane (136 mg, 0.32 mmol, 1.1 equiv). After stirring at room temperature for 45 minutes the reaction was quenced with a 1:1 mixture of saturated sodium thiosulfate and saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted two more times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. In a separate flask dimethyl methylphosphonoacetate (187 μL, 1.73 mmol, 15 equiv) in THF (1 mL) was being deprotonated at – 78C with BuLi (1.6M in hexanes, 0.93 mL, 1.50 mmol, 13 equiv). After stirring for 30 minutes at –78C, the aldehyde obtained from the Dess-Martin oxidation dissolved in THF (1mL) was added to the reaction mixture. Upon completion of the addition the cold bath was replaced with an ice bath and the reaction mixture was quenched 20 minutes later by the addition of saturated ammonium chloride solution. This solution was extracted four times with ethyl acetate, dried over Na_2SO_4 and evaporated. This crude mixture was then subjected to the same Dess-Martin conditions as described above to afford phosphonate ester **12** as a crude product that was used directly in the next reaction.

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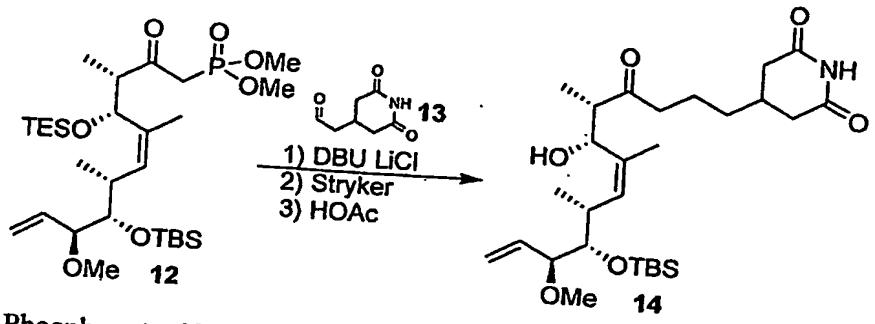
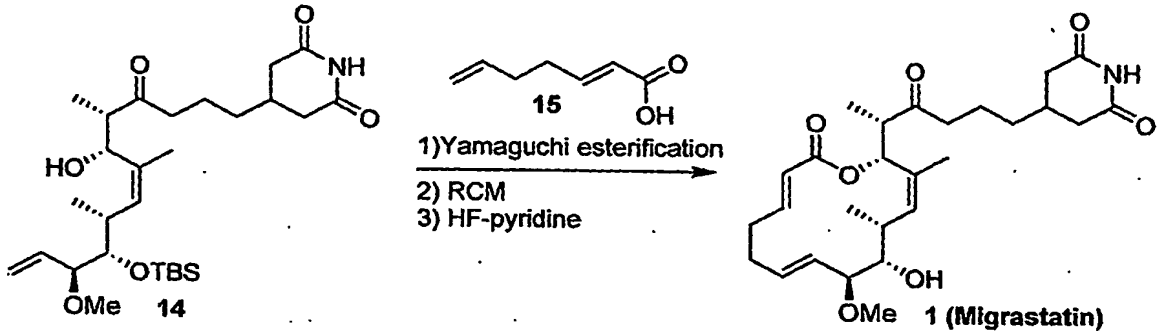


[0341] Phosphonate **12** was dissolved in dry acetonitrile (5 mL) and treated with LiCl (25mg, 0.58 mmol, 2 equiv) and DBU (87 μL, 0.58 mmol, 2 equiv). After 10 minutes aldehyde **13** (136 mg, 0.88 mmol, 3 equiv, Egawa, Y.; Suzuki, M.; Okuda, T. *Chem. Pharm. Bull.* **1963**, *11*, 589) dissolved in 1mL acetonitrile was added. The mixture was allowed to stir at room temperature for 45 minutes before being quenched by the addition of saturated ammonium chloride and extracted three times with ethyl acetate. Following drying over Na_2SO_4 and evaporation the crude mixture was chromatographed over a column of silica gel (gradient elution, 20-33% EtOAc/Hexanes) to afford the corresponding enone (105 mg, 0.165 mmol, 57% yield over 4 steps) as a clear oil. This enone (101 mg, 0.159 mmol, 1 equiv) was dissolved in dry toluene and treated with Stryker reagent (156 mg, 0.079 mmol, 0.5 equiv, Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291). After 3.5 hours at room temperature hexanes was added (5 mL) and the crude mixture stirred under air for 20 minutes before being concentrated and chromatographed over a column of silica gel (gradient elution, 15-33% EtOAc/Hexanes) to afford the corresponding ketone. This ketone was stirred in a 3:1:1 mixture of HOAc/THF/Water for 2 hours before being quenched by the addition of solid Na_2CO_3 and 1N NaOH. This mixture was extracted four times with ethyl acetate, dried over Na_2SO_4, evaporated and chromatographed over a column of silica gel (gradient elution, 20-50% EtOAc/Hexanes) to afford seco-alcohol **14** (68 mg, 0.130 mmol, 82% yield over 2 steps).

[0342] **Compound 14**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 5.63-5.56 (m, 1H), 5.48 (d, J = 9.3, 1H), 5.33 (dd, J = 10.3, 1.7, 1H), 5.27 (dd, J = 17.2, 1.3, 1H), 4.95 (d, J = 9.8, 1H), 4.41-4.35 (m, 2H), 3.19 (s, 3H), 2.79-2.63 (m, 4H), 2.58-2.54 (m, 2H), 2.29-2.23 (m, 2H), 2.18-2.10 (m, 1H), 1.95 (br s, 1H), 1.66 (d, J = 1.0, 3H), 1.66-1.59 (m, 2H), 1.42-1.37 (m, 2H), 0.90 (s, 9H), 0.88 (d, J = 6.6, 3H), 0.87 (d, J = 7.1, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 214.01, 172.21, 135.51, 134.72, 131.56, 119.19, 86.30, 78.26, 71.69, 55.98, 48.87, 42.70, 37.73, 37.70, 34.08, 33.26, 30.32, 26.11, 20.07, 18.55, 17.35, 13.87, 13.63, –3.79, –

4.90; MS (ESI) 546 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{28}H_{49}NO_6NaSi$ [M+Na$^+$] 546.3227, found 546.3227.

[0343] Step 5: Preparation of Migrastatin (1):



[0344] The yamaguchi anhydride was prepared by stirring dienoic acid **15** (68 mg, 0.54 mmol, 1equiv, Katzenellenbogen, J. A.; Crumrine, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 4925) along with hunigs base (89 μL, 0.51 mmol, 0.95 equiv) and yamaguchi reagent (84 μL, 0.54 mmol, 1 equiv, Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989) for 3 hours at room temperature. An aliquot (300 mL, 3 equiv) of this anhydride was added to a mixture of alcohol **14** (28 mg, 0.053 mmol, 1 equiv) and pyridine (17 μL, 0.212 mmol, 4 equiv) in toluene (100 μL). This reaction mixture was stirred at room temperature for 22 hours at which point it was loaded directly onto a silica and chromatographed (gradient elution, 10-33% EtOAc/Hexanes) to afford the corresponding ester (22mg, 0.035 mmol, 66% yield). This ester (10.5 mg, 0.0166 mmol, 1 equiv) was dissolved in toluene (30mL) and heated to reflux before adding second-generation Grubbs catalyst (2.8 mg, 0.00332 mmol, 0.2 equiv, Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953). After 10 minutes at reflux the reaction mixture was cooled to room temperature, passed through a silica plug using 25% EtOAc/Hexanes as the eluent and evaporated. The resulting oil was further chromatographed over a column of silica gel (gradient elution, 16-50% EtOAc/Hexanes) to afford the desired macrocycle (7 mg, 0.0116 mmol, 70% yield). The macrocycle (13 mg, 0.0215 mmol, 1 equiv) was dissolved in THF (1.25 mL) and treated with HF-pyridine (0.25 mL). This reaction mixture was stirred at room temperature for 7.5 hours before being quenched by the addition of MeOTMS (2.5 mL). Evaporation and chromatography over a column of silica gel (gradient elution, 33-66% EtOAc/Hexanes) afforded Migrastatin (**1**, 10mg, 0.0204 mmol, 95% yield) as a clear oil.

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[0345] **Compound 1 (Migrastatin)**: $[\alpha]_D$ +12.6° (c 0.50, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 6.49 (ddd, J = 15.7, 10.5, 3.7, 1H), 5.64 (dd, J = 10.7, 1.2, 1H), 5.58 (dd, J = 15.8, 1.2, 1H), 5.54-5.48 (m, 1H), 5.24 (dd, J = 15.5, 4.7, 1H), 5.08 (d, J = 10.0, 1H), 3.47 (dd, J = 8.7, 4.8, 1H), 3.30 (s, 3H), 3.03 (dd, J = 8.7, 1.7, 1H), 2.99-2.87 (m, 2H), 2.80 (br s, 1H), 2.73-2.68 (m, 2H), 2.50 (app t, J = 6.9, 2H), 2.44-2.39 (m, 2H), 2.28-2.18 (m, 4H), 2.15-2.08 (m, 1H), 1.86 (d, J = 1.2, 3H), 1.69-1.55 (m, 2H), 1.41-1.30 (m, 2H), 1.12 (d, J = 7.2, 3H), 0.96 (d, J = 6.9, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 210.88, 171.78, 163.86, 150.01, 132.99, 131.17, 130.46, 127.87, 122.08, 82.39, 77.92, 76.92, 56.93, 51.18, 39.88, 37.68, 37.66, 34.12, 31.93, 31.08, 30.34, 25.99, 20.09, 13.39; MS (ESI) 512 [M+Na^+]; HRMS (FAB) calcd. for $C_{27}H_{39}NO_7Na$ [M+Na^+] 512.2604, found 512.2624.

[0346] The ^{1}H NMR spectrum corresponding to compound **1** is shown in Figure 1A. Figure 1B depict a ^{1}H NMR spectrum of naturally occurring Migrastatin.

[0347] **Biological Data**

[0348] Tube formation assay:

[0349] A protocol was designed based on the instructions from the provider (BD Bioscience, San Jose, CA). Briefly, wells of a 48 well culture dish were covert with 150 µL matrigel and the matrigel was gelatinized for 30 min at 37 °C. A 80-90% confluent HUVEC (BD Bioscience, San Jose, CA) culture was trypsin treated, the detached cells were collected by centrifugation and resuspended in EGM-2 media (BD Bioscience, San Jose, CA). Cell concentration was adjusted to 100.000 cells/mL. 400 µL of the cell suspension were filled in the matrigel coated wells, and a solution of the inhibitor was added to the intended final concentration. The plates were incubated at 37 °C with 5 % CO_2 for 16 – 18 h. Media was removed, and the matrigel surface was washed twice with 500 µL PBS before cells were labeled with 250 µL 8 µM Calcein AM (Pierce, Rockford, IL) in PBS for 30 min at 37 °C. After two additional washing steps (500 µL PBS) cells were visualized under an inverted microscope. Fluorescence was excited at 488 nm and recorded at 538 nm. The minimum effect concentration was defined as the minimal inhibitor concentration that caused a definite disturbance of the complexity of the formed tube network.

[0350] Wound healing assay

[0351] The wound healing assay was performed based on the method described by Nakae *et al.* (Nakae *et al., J. Antibiotics* (2000), 53, 1130-1136). Briefly, adherent cells were grown in a suitable media to confluence (*e.g.* KYSE-520 cells in RPMI-1640 with 10 % FBS). Cells were starved for 24 h in serum free media. A scratch (ca. 0.5 mm) was applied and the cell layer was washed twice with PBS after removal of the media. Fresh, serum free media with the test compound at the desired concentration was added and the cells were incubated for 28 to 30 h at 37 °C, 5 % CO_2. The scratch size was compared to that observed for cells exposed to 100μM Migrastatin. Test compounds associated with a scratch size equal to or larger than that observed for cells exposed to 100μM Migrastatin were deemed to have cell migration inhibitory activity at least equal to Migrastatin.

[0352] Chamber cell migration assay

[0353] Cells were grown in an appropriate media to 70 to 80 % confluence and incubated in serum and growth factor free media for 24 h. Cells were detached by trypsin treatment, collected by centrifugation and resuspended in serum free media to a final concentration of 150,000 cells/mL. 400 μL of the cell suspension were loaded into a fibronectin coated insert for 24 well multidishes. 750 μL fully supplemented media were applied to the compartment under the insert. To both chambers the inhibitor was added at the intended concentration and the plates were incubated for 36 h at 37 °C, 5 % CO_2. The media from both chambers was aspirated, the lower section was filled with 300 μL CyQuant assay solution (Molecular Probes, Eugene, OR), and incubated at room temperature for 5min. The resulting CyQuant assay solution was transferred to the cavities of a 96 well microtiter plate and the fluorescence signal was recorded in an appropriate reader. The CyQuant dye forms a highly fluorescent complex with DNA, thus the fluorescence signal is proportional to the number of cells that migrated throught he membrane in the presence of the test compound (N^{inh}). A positive control (i.e., without a test compound in the growth media) was carried out according to the procedure described above, except that no test compound was added. The positive control fluorescent reading correlates with the number of cells that migrate through the membrane in the absence of inhibitor (N^{+}). A negative control (i.e., without a test compound and without attractants (e.g., growth factors, serum) in the growth media) was carried out according to the procedure described above, except that no test compound and attractants were added. The negative control fluorescent reading

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correlates with the number of cells that migrate through the membrane through non-directed processes (N^-). The anti-migratory effect of a test compound is determined by the ratio ($N^{inh} - N^-$) / ($N^+ - N^-$).

[0354] Table 1: Tube formation assay

Substance	**Minimum effect concentration**
Migrastatin	100 µM
Migrastatin derivative 1	200 µM
Migrastatin derivative 2	50 µM
Migrastatin derivative 3	10 µM

Tested concentrations: 200, 100, 50, 25, 10 µM

[0355] Table 2: Scratch Assay

Substance	**Minimum effect concentration**
Migrastatin	100 µM
Migrastatin derivative 1	100 µM
Migrastatin derivative 2	25 µM

Tested concentrations: 200, 100, 50, 25, 10 µM

[0356] **Table 3: Chamber Assay**

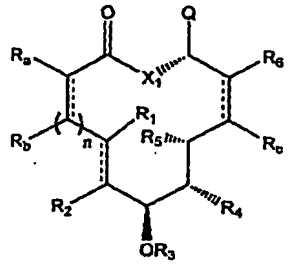
Substance	**IC_{50}**
Migrastatin	200 µM

Tested concentrations: 200, 100, 50, 25, 10 µM

CLAIMS

We claim:

1. A compound having the structure:



wherein R_1 and R_2 are each independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{1A}$; $-NO_2$, $-COR^{1A}$, $-CO_2R^{1A}$, $-NR^{1A}C(=O)R^{1B}$, $-NR^{1A}C(=O)OR^{1B}$, $-CONR^{1A}R^{1B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{1A}$; wherein W is independently -O-, -S- or $-NR^{1C}$-, wherein each occurrence of R^{1A}, R^{1B} and R^{1C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_1 and R_2, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_3 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 is hydrogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_6 is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{6A}$, $-NO_2$, $-COR^{6A}$, $-CO_2R^{6A}$, $-NR^{6A}C(=O)R^{6B}$, $-NR^{6A}C(=O)OR^{6B}$, $-CONR^{6A}R^{6B}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{6A}$; wherein W is independently -O-, -S- or $-NR^{6C}$-, wherein each occurrence of R^{6A}, R^{6B} and R^{6C} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_6, taken together with Rc, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_a and each occurrence of R_b are independently hydrogen, halogen, -CN, $-S(O)_{1-2}R^{a1}$, $-NO_2$, $-COR^{a1}$, $-CO_2R^{a1}$, $-NR^{a1}C(=O)R^{a2}$, $-NR^{a1}C(=O)OR^{a2}$, $-CONR^{a1}R^{a2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, R^{a2} and R^{a3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

R_c is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{c1}$, $-NO_2$, $-COR^{c1}$, $-CO_2R^{c1}$, $-NR^{c1}C(=O)R^{c2}$, $-NR^{c1}C(=O)OR^{c2}$, $-CONR^{c1}R^{c2}$; an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1}, R^{c2} and R^{c3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an alicyclic, heteroalicyclic, aryl or heteroaryl moiety;

n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}$-, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

with the proviso that the compound does not have the structure:

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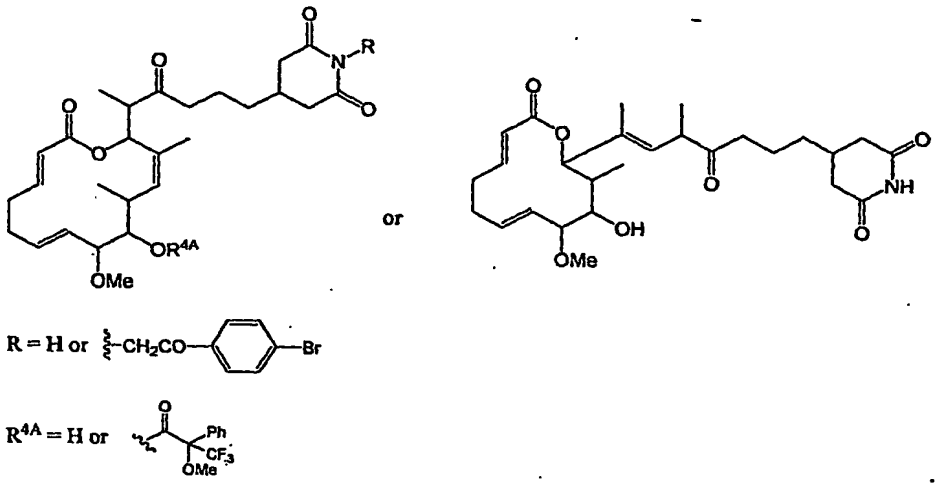

2. The compound of claim 1, wherein:

R_1 and R_2 are each independently hydrogen or substituted or unsubstituted lower alkyl;

R_3 is hydrogen, or substituted or unsubstituted lower alkyl or aryl; a prodrug moiety or an oxygen protecting group;

R_4 is halogen, OR^{4A}, $NR^{4A}R^{4B}$; wherein R^{4A} and R^{4B} are independently hydrogen, or substituted or unsubstituted lower alkyl; a prodrug moiety, a nitrogen protecting group or an oxygen protecting group; or R^{4A} and R^{4B}, taken together with the nitrogen atom to which they are attached, form a heterocyclic or heteroaryl moiety;

R_5 and R_6 are each independently hydrogen or substituted or unsubstituted lower alkyl;

R_a and each occurrence of R_b are independently hydrogen, halogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{a1}$; wherein W is independently -O-, -S- or $-NR^{a3}$-, wherein each occurrence of R^{a1}, and R^{a3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; or R_a and the adjacent occurrence of R_b, taken together, form an epoxide or a substituted or unsubstituted cyclopropyl moiety;

R_c is hydrogen, halogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, or $-WR^{c1}$; wherein W is independently -O-, -S- or $-NR^{c3}$-, wherein each occurrence of R^{c1} and R^{c3} is independently hydrogen, or an alkyl, heteroalkyl, cycloalkyl,

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heterocycloalkyl, aryl or heteroaryl moiety; or R_c, taken together with R_6, forms an epoxide or a substituted or unsubstituted cyclopropyl moiety;

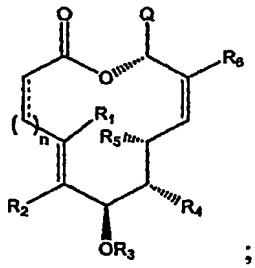
n is an integer from 1 to 5;

X_1 is O, S, NR^{X1} or $CR^{X1}R^{X2}$; wherein R^{X1} and R^{X2} are independently hydrogen, halogen, substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, or a nitrogen protecting group;

Q is hydrogen, halogen, -CN, $-S(O)_{1-2}R^{Q1}$, $-NO_2$, $-COR^{Q1}$, $-CO_2R^{Q1}$, $-NR^{Q1}C(=O)R^{Q2}$, $-NR^{Q1}C(=O)OR^{Q2}$, $-CONR^{Q1}R^{Q2}$, an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety, or $-WR^{Q1}$; wherein W is independently -O-, -S- or $-NR^{Q3}-$, wherein each occurrence of R^{Q1}, R^{Q2} and R^{Q3} is independently hydrogen, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof.

3. The compound of claim 2, wherein R_a, R_b and R_c are each hydrogen, X_1 is O and the compound has the structure:

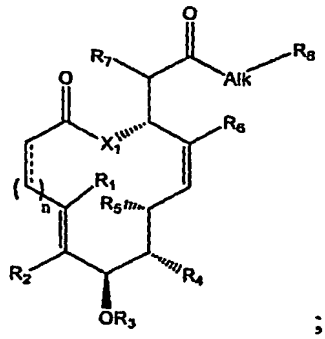


;

wherein R_1-R_6, n and Q are as defined in claim 2; and

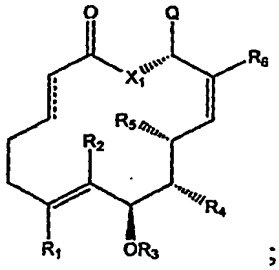
pharmaceutically acceptable derivatives thereof.

4. The compound of claim 2, wherein R_a, R_b and R_c are each hydrogen, X_1 is O, Q is a carbonyl-containing moiety and the compound has the structure:



wherein R_1-R_6, n and X_1 are as defined in claim 2; R_7 is a substituted or unsubstituted lower alkyl or heteroalkyl moiety; R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl.

5. The compound of claim 2, wherein R_a, R_b and R_c are each hydrogen, n is 3 and the compound has the structure:



wherein R_1-R_6, Q and X are as defined in claim 2.

6. The compound of claim 2, wherein R_a, R_b and R_c are each hydrogen, X_1 is O, n is 3, Q is a carbonyl-containing moiety, and the compound has the structure:

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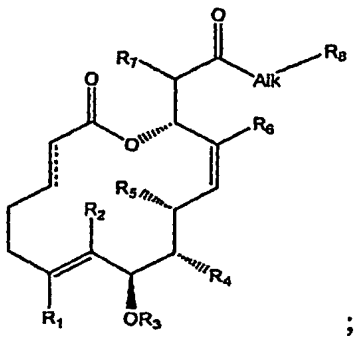

;

wherein R_1-R_6 are as defined in claim 2; R_7 is a substituted or unsubstituted lower alkyl or heteroalkyl moiety; R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety; and Alk is a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; and R_8 is a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety.

7. The compound of any one of claims 1-6, wherein R_1 and R_2 are each hydrogen.

8. The compound of any one of claims 1-6, wherein R_5 and R_6 are each methyl.

9. The compound of any one of claims 1-6, wherein R_3 is lower alkyl.

10. The compound of claim 9, wherein R_3 is methyl.

11. The compound of any one of claims 1-6, wherein R_4 is OH, NH_2 or halogen.

12. The compound of claim 4 or 6, wherein R_7 is lower alkyl.

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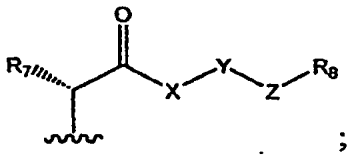
13. The compound of claim 12, wherein R_7 is methyl.

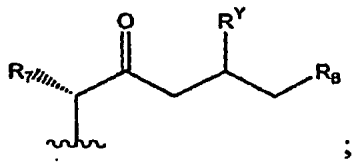
14. The compound of any one of claims 1-3 and 5, wherein Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, -NR^{Z1}-, –$CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, C=N(R^{Y1}) or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

15. The compound of claim 14, wherein Q has the structure:



;

wherein R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R_8 is a substituted or unsubstituted carbocyclic, heterocyclic, aryl or heteroaryl moiety; and R^Y is hydrogen, halogen, -OR^{Y1} or –$NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety.

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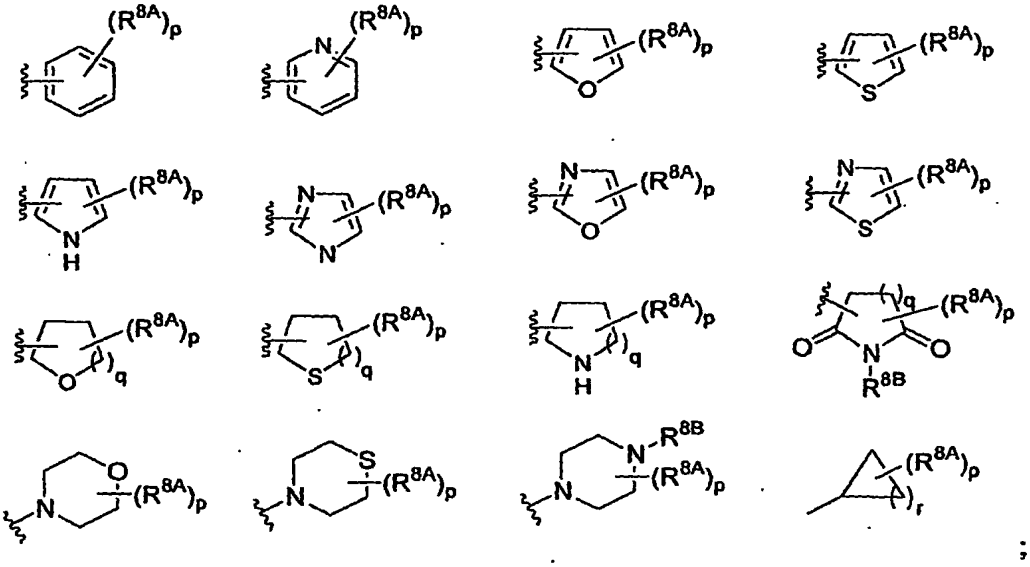
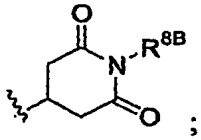
16. The compound of any one of claims 4, 6, 14 and 15, wherein R_8 is one of:



wherein p is an integer from 0 to 5; q is 1 or 2, r is an integer from 1 to 6; each occurrence of R^{8A} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl, $-OR^{8C}$, $-SR^{8C}$, $-N(R^{8C})_2$, $-SO_2N(R^{8C})_2$, $-(C=O)N(R^{8C})_2$, halogen, -CN, $-NO_2$, $-(C=O)OR^{8C}$, $-N(R^{8C})(C=O)R^{8D}$, wherein each occcurrence of R^{8C} and R^{8D} is independently hydrogen, lower alkyl, lower heteroalkyl, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl; and each occurrence of R^{8B} is independently hydrogen or lower alkyl.

17. The compound of claim 16, wherein R_8 has the structure:



wherein R^{8B} is hydrogen or lower alkyl.

18. The compound of claim 1, 2, 3 or 4, wherein n is 3.

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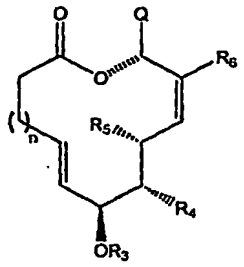
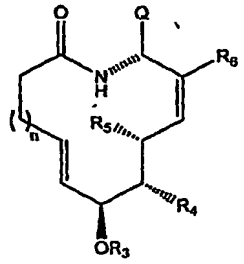
19. The compound of claim 2 wherein R_a, R_b and R_c are each hydrogen, X_1 is O, and the compound has the structure:



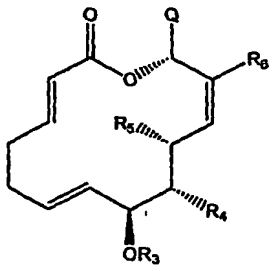
wherein R_3-R_6, n and Q are as defined in claim 2; and pharmaceutically acceptable derivatives thereof.

20. The compound of claim 2 wherein R_a, R_b and R_c are each hydrogen, X_1 is NH, and the compound has the structure:



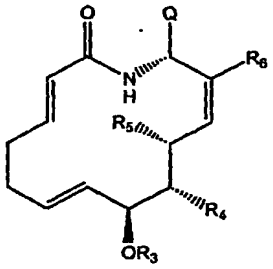
wherein R_3-R_6, n and Q are as defined in claim 2; and pharmaceutically acceptable derivatives thereof.

21. The compound of claim 2 wherein the compound has the structure:



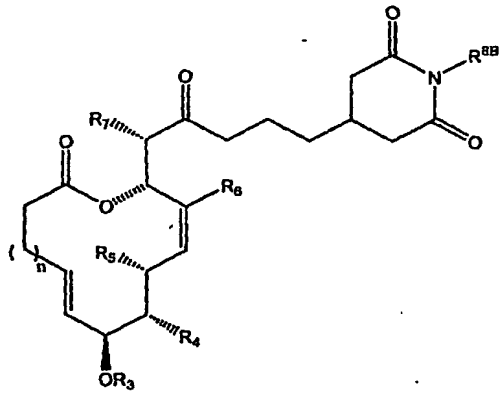
wherein R_3-R_6 and Q are as defined in claim 2; and pharmaceutically acceptable derivatives thereof.

22. The compound of claim 2 wherein the compound has the structure:



wherein R_3-R_6 and Q are as defined in claim 2; and pharmaceutically acceptable derivatives thereof.

23. The compound of claim 2 wherein the compound has the structure:



wherein R_3-R_6 and n are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl; and pharmaceutically acceptable derivatives thereof.

24. The compound of claim 2 wherein the compound has the structure:

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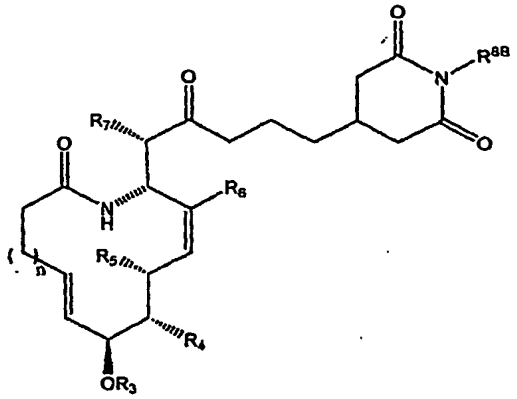
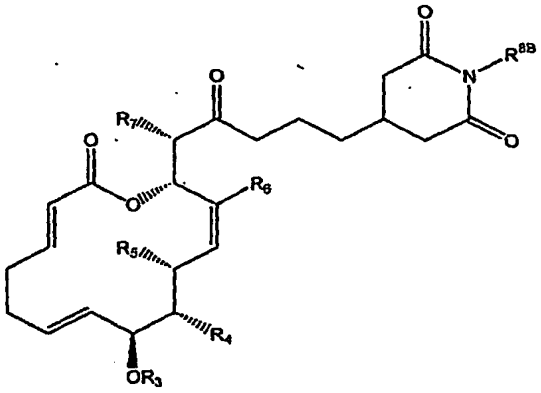


wherein R_3-R_6 and n are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl; and pharmaceutically acceptable derivatives thereof.

25. The compound of claim 2 wherein the compound has the structure:



wherein R_3-R_6 are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl; and pharmaceutically acceptable derivatives thereof.

26. The compound of claim 2 wherein the compound has the structure;

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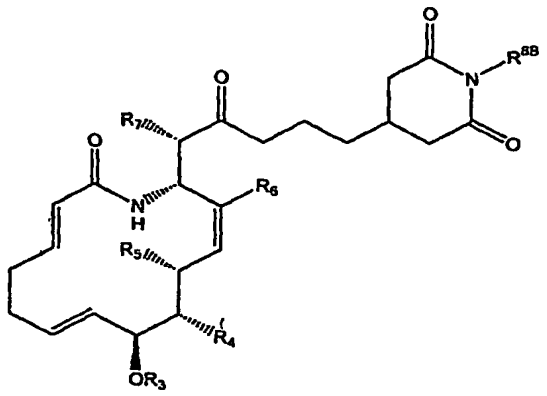
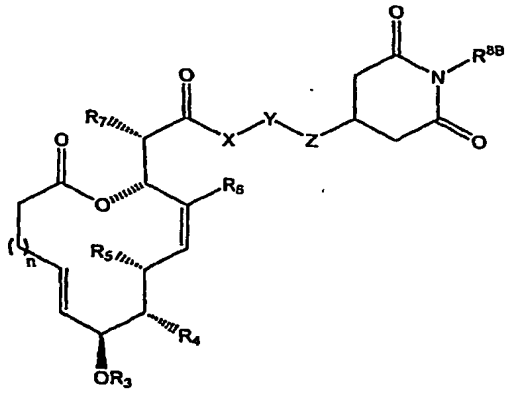


wherein R_3-R_6 are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; and R^{8B} is hydrogen or lower alkyl; and pharmaceutically acceptable derivatives thereof.

27. The compound of claim 2 wherein the compound has the structure:



wherein R_3-R_6 and n are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}-$, $-CHOR^{Z1}$, $-CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from

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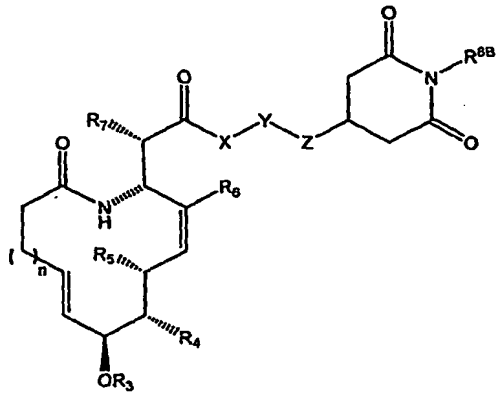
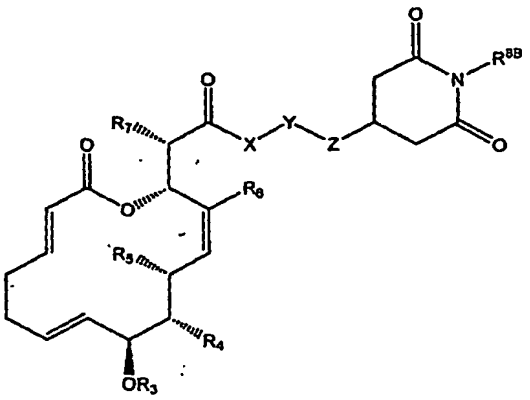
F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

28. The compound of claim 2 wherein the compound has the structure:



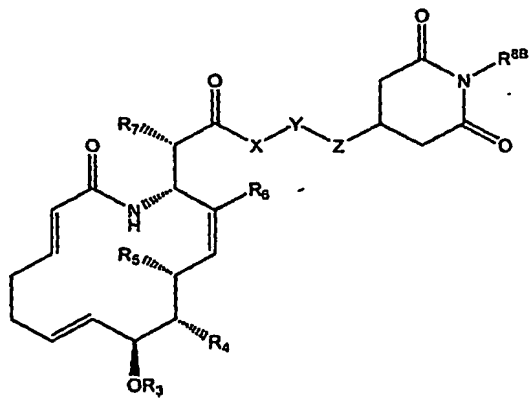
wherein R_3-R_6 and n are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}$-, $-CHOR^{Z1}$, $-CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

29. The compound of claim 2 wherein the compound has the structure:



wherein R_3-R_6 are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, -NR^{Z1}-, –$CHOR^{Z1}$, -$CHNR^{Z1}R^{Z2}$, C=S, C=N(R^{Y1}) or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

30. The compound of claim 2 wherein the compound has the structure:



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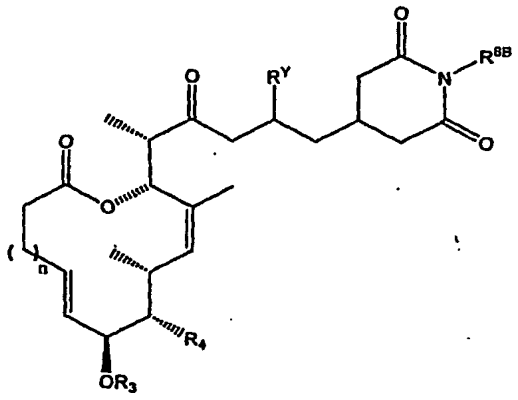
wherein R_3-R_6 are as defined in claim 2; R_7 is a substituted or unsubstituted, linear or branched, cyclic or acyclic lower alkyl moiety; R^{8B} is hydrogen or lower alkyl; and X, Y and Z are independently a bond, -O-, -S-, -C(=O)-, $-NR^{Z1}-$, $-CHOR^{Z1}$, $-CHNR^{Z1}R^{Z2}$, C=S, $C=N(R^{Y1})$ or –CH(Hal); or a substituted or unsubstituted C_{0-6}alkylidene or C_{0-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein Hal is a halogen selected from F, Cl, Br and I; and each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; or R^{Z1} and R^{Z2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

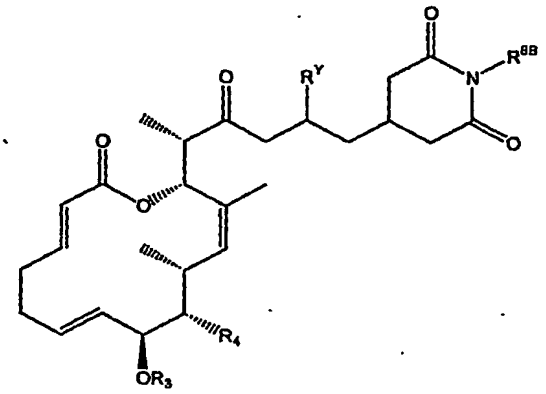
31. The compound of any one of claims 27-30 wherein –X-Y-Z together represents the moiety $-CH_2$-Y-CH_2-; wherein Y is $-CHOR^{Y1}$, $-CHNR^{Y1}R^{Y2}$, C=O, C=S, $C=N(R^{Y1})$ or –CH(Hal); wherein Hal is a halogen selected from F, Cl, Br and I; and R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

32. The compound of claim 2 wherein the compound has the structure:



wherein n, R_3 and R_4 are as defined in claim 2; R^{8B} is hydrogen or lower alkyl; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

33. The compound of claim 2 wherein the compound has the structure:



wherein R_3 and R_4 are as defined in claim 2; R^{8B} is hydrogen or lower alkyl; and R^Y is hydrogen, halogen, $-OR^{Y1}$ or $-NR^{Y1}NR^{Y2}$; wherein R^{Y1} and R^{Y2} are independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl, or R^{Y1} and R^{Y2}, taken together with the nitrogen atom to which they are attached, for a heterocyclic or heteroaryl moiety; and pharmaceutically acceptable derivatives thereof.

34. A pharmaceutical composition comprising;

a compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier or diluent.

35. The pharmaceutical composition of claim 34 wherein the compound is present in an amount effective to inhibit the metastasis of tumor cells.

36. The pharmaceutical composition of claim 34 wherein the compound is present in an amount effective to inhibit angiogenesis.

37. The composition of claim 34, further comprising a cytotoxic agent.

38. The composition of claim 34, wherein the cytotoxic agent is an anticancer agent.

39. The composition of claim 34, further comprising a palliative agent.

40. A method for preventing metastasis of tumor cells in a subject comprising:

administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier.

41. The method of claim 40, wherein the method is used to prevent metastasis of prostate, breast, colon, bladder, cervical, skin, testicular, kidney, ovarian, stomach, brain, liver, pancreatic or esophageal cancer or lymphoma, leukemia, or multiple myeloma.

42. The method of claim 41, wherein the cancer is a solid tumor.

43. The method of claim 41, further comprising administering a cytotoxic agent.

44. The method of claim 43, wherein the cytotoxic agent is an anticancer agent.

45. The method of claim 41, further comprising administering a palliative agent.

46. A method for inhibiting angiogenesis in a subject comprising:

administering to a subject in need thereof an angiogenesis inhibiting amount of the compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier.

47. The method of claim 46, wherein the angiogenesis causes an angiogenesis dependent disease.

48. The method of claim 47, wherein the angiogenesis dependent disease is ocular angiogenic diseases, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasias, rubeosis, solid tumors, blood born tumors, leukemias, tumor metastases, benign tumors, acoustic neuromas, neurofibromas, trachomas, pyogenic granulomas, rheumatoid arthritis, psoriasis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, or wound granulation.

49. A method of treating a non-tumor blood condition associated with angiogenesis in a subject comprising:

administering to a subject in need thereof an angiogenesis inhibiting amount of the compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier.

50. The method of claim 49 wherein the undesired angiogenesis occurs in polyarteritis, sickle cell anemia, vein occlusion, artery occlusion, carotid obstructive disease, Osler-Weber-Rendu disease or atherosclerosis.

51. A method of treating an immune disease associated with angiogenesis in a subject comprising:

administering to a subject in need thereof an angiogenesis inhibiting amount of the compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier.

52. The method of claim 51 wherein the undesired angiogenesis occurs in rheumatoid arthritis, systemic lupus, in osteoarthritis or acquired immune deficiency syndrome.

53. A method of treating an infection associated with angiogenesis in a subject comprising:

administering to a subject in need thereof an angiogenesis inhibiting amount of the compound of any one of claims 1-33; and

a pharmaceutically acceptable carrier.

54. The method of claim 53 wherein the undesired angiogenesis occurs in sysphilis, Mycobacteria infections, Herpes simplex infections, Herpes zoster infections, protazoan infections, in toxoplasmosis or Bartonellosis.

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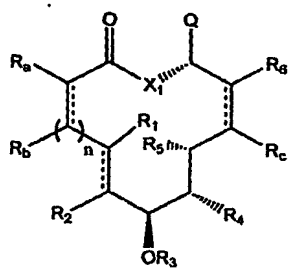
ABSTRACT

The present invention provides compounds having formula (I):



and additionally provides methods for the synthesis thereof, compositions thereof, and methods for the use thereof in the treatment of various disorders including cancer, metastasis and disorders involving increased angiogenesis, wherein R_1-R_6, R_a-R_c, Q and n are as defined herein.

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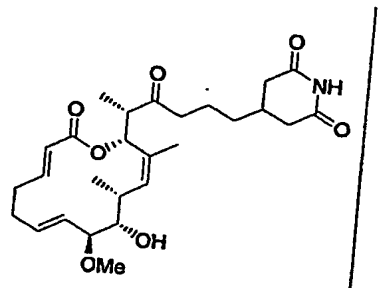

(+)-Migrastatin

FIG. 1A

FIG. 1B

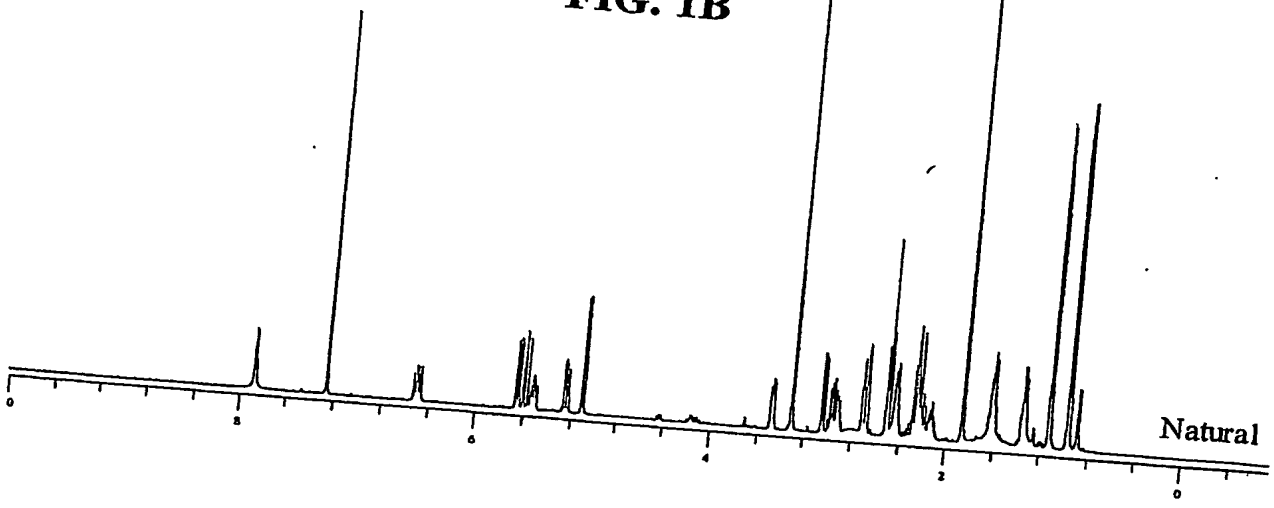

Figure 1

APPENDIX A

FDA Approved Oncology Drugs

Drug	Drug Trade Name	Approved Use	Manufacturer/Distributor	Ap
alitretinoin	Panretin	Topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.	Ligand Pharmaceuticals	Fe 19
allopurinol	Zyloprim	Patients with leukemia, lymphoma and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.	GlaxoSmithKline	Ma 19
altretamine	Hexalen	Single agent palliative treatment of patients with persistent or recurrent ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent based combination.	US Bioscience	De 19
amifostine	Ethyol	To reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer	US Bioscience	De 19
amifostine	Ethyol	Reduction of platinum toxicity in non-small cell lung cancer	US Bioscience	Ma 19
amifostine	Ethyol	To reduce post-radiation xerostomia for head and neck cancer where the radiation port includes a substantial portion of the parotid glands.	US Bioscience	Jur 19
anastrozole	Arimidex	for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	AstraZeneca	Sep 20
anastrozole	Arimidex	Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.	AstraZeneca Pharmaceuticals	De 19
anastrozole	Arimidex	For first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	AstraZeneca Pharmaceuticals	Sep 20
arsenic trioxide	Trisenox	Second line treatment of relapsed or refractory APL following ATRA plus an anthracycline.	Cell Therapeutic	Sep 20
bexarotene	Targretin	For the treatment by oral capsule of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals	De 19
bexarotene	Targretin	For the topical treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.	Ligand Pharmaceuticals	Jun 20
bleomycin	Blenoxane	Sclerosing agent for the treatment of malignant pleural effusion (MPE) and prevention of recurrent pleural effusions.	Bristol-Myers Squibb	Feb 19

busulfan intravenous	Busulfex	Use in combination with cyclophoshamide as conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.	Orphan Medical, Inc	Fel 19
busulfan oral	Myleran	Chronic Myelogenous Leukemia- palliative therapy	GlaxoSmithKline	Jun 19
capecitabine	Xeloda	Treatment of metastatic breast cancer resistant to both paclitaxel and an anthracycline containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents	Roche	Apı 199
capecitabine	Xeloda	Treatment in combination with docetaxel of patients with metastatic breast cancer after failure of prior anthracycline containing chemotherapy	Roche	Sep 200
capecitabine	Xeloda	Initial therapy of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5_FU/LV has not been demonstrated with Xeloda monotherapy.	Roche	Apı 200
carboplatin	Paraplatin	Initial chemotherapy of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents.	Bristol-Myers Squibb	Jul 199
carboplatin	Paraplatin	Palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.	Bristol-Myers Squibb	Mar 198
carmustine with Polifeprosan 20 Implant	Gliadel Wafer	For use in addition to surgery to prolong survival in patients with recurrent glioblastoma multiforme who qualify for surgery.	Guilford Pharmaceuticals Inc.	Sep 199
celecoxib	Celebrex	Reduction of polyp number in patients with the rare genetic disorder of familial adenomatous polyposis.	Searle	Dec 199
chlorambucil	Leukeran	Chronic Lymphocytic Leukemia- palliative therapy	GlaxoSmithKline	Mar 195
chlorambucil	Leukeran	Non-Hodgkin's Lymphoma	GlaxoSmithKline	Mar 195
cisplatin	Platinol	Metastatic testicular-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors whoc have	Bristol-Myers Squibb	Dec

		already received appropriate surgical and/or radiotherapeutic procedures. An established combination therapy consists of Platinol, Blenoxane and Velbam.		1
cisplatin	Platinol	Metastatic ovarian tumors - in established combination therapy with other approved chemotherapeutic agents: Ovarian-in established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Platinol and Adriamycin. Platinol, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Platinol therapy.	Bristol-Myers Squibb	D 19
cisplatin	Platinol	as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.	Bristol-Myers Squibb	A 19
cladribine	Leustatin, 2-CdA	Treatment of active hairy cell leukemia.	R.W. Johnson Pharmaceutical Research Institute	Fe 19
cytarabine liposomal	DepoCyt	Intrathecal therapy of lymphomatous meningitis	Skye Pharmaceuticals	A 19
daunorubicin liposomal	DanuoXome	First line cytotoxic therapy for advanced, HIV related Kaposi's sarcoma.	Nexstar, Inc.	A 19
daunorubicin, daunomycin	Daunorubicin	Leukemia/myelogenous/monocytic/erythroid of adults/remission induction in acute lymphocytic leukemia of children and adults.	Bedford Labs	Ja 19
daunorubicin, daunomycin	Cerubidine	In combination with approved anticancer drugs for induction of remission in adult ALL.	Wyeth Ayerst	M 19
dexrazoxane	Zinecard	Prevention of cardiomyopathy associated with doxorubicin administration	Pharmacia & Upjohn Company	M 19
dexrazoxane	Zinecard	reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy.	Pharmacia & Upjohn Company	O 20
		For the treatment of locally advanced or		

docetaxel	Taxotere	metastatic breast cancer which has progressed during anthracycline-based treatment or relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceutical	Ju 1!
docetaxel	Taxotere	Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.	Aventis Pharmaceutical	M 1!
docetaxel	Taxotere	For locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.	Aventis Pharmaceutical	D 1!
docetaxel	Taxotere	in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer	Aventis Pharmaceutical	N 2(
doxorubicin	Adriamycin PFS Injectionintravenous injection	Antibiotic, antitumor agent.	Pharmacia & Upjohn Company	D 1!
doxorubicin liposomal	Doxil	Treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.	Sequus Pharmaceuticals, Inc.	N 1!
doxorubicin liposomal	Doxil	Treatment of metastatic carcinoma of the ovary in patient with disease that is refractory to both paclitaxel and platinum based regimens	Sequus Pharmaceuticals, Inc.	Ju 1!
Elliott's B Solution	Elliott's B Solution	Diluent for the intrathecal administration of methotrexate sodium and cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.	Orphan Medical, Inc	Se 1!
epirubicin	Ellence	A component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.	Pharmacia & Upjohn Company	Se 1!
estramustine	Emcyt	palliation of prostate cancer	Pharmacia & Upjohn Company	D 1!
etoposide phosphate	Etopophos	Management of refractory testicular tumors, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squibb	M 1!
etoposide phosphate	Etopophos	Management of small cell lung cancer, first-line, in combination with other approved chemotherapeutic agents.	Bristol-Myers Squibb	M 1!
etoposide phosphate	Etopophos	Management of refractory testicular tumors and small cell lung cancer.	Bristol-Myers Squibb	Fe 1!
etoposide,		In combination with other approved chemotherapeutic agents as first line		D

VP-16	Vepesid	treatment in patients with small cell lung cancer.	Bristol-Myers Squibb	19
etoposide, VP-16	Vepesid	Refractory testicular tumors-in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic and radiotherapeutic therapy.	Bristol-Myers Squibb	N 19
exemestane	Aromasin	Treatment of advance breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.	Pharmacia & Upjohn Company	O 19
fludarabine	Fludara	Palliative treatment of patients with B-cell lymphocytic leukemia (CLL) who have not responded or have progressed during treatment with at least one standard alkylating agent containing regimen.	Berlex Laboratories Inc.	A 19
fluorouracil, 5-FU	Adrucil	prolong survival in combination with leucovorin	ICN Puerto Rico	A 19
fulvestrant	Faslodex	the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy	IPR	A 20
gemcitabine	Gemzar	Treatment of patients with locally advanced (nonresectable stage II or III) or metastatic (stage IV) adenocarcinoma of the pancreas. Indicated for first-line treatment and for patients previously treated with a 5-fluorouracil-containing regimen.	Eli Lilly	M 19
gemcitabine	Gemzar	For use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.	Eli Lilly	A 19
gemtuzumab-ozogamicin	Mylotarg	Treatment of CD33 positive acute myeloid leukemia in patients in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy.	Wyeth Ayerst	M 20
goserelin acetate	Zoladex Implant	Palliative treatment of advanced breast cancer in pre- and perimenopausal women.	AstraZeneca Pharmaceuticals	D 19
hydroxyurea	Hydrea	Decrease need for transfusions in sickle cell anemia	Bristol-Myers Squibb	F 19
idarubicin	Idamycin	For use in combination with other approved antileukemic drugs for the treatment of acute myeloid leukemia (AML) in adults.	Adria Laboratories	S 19
idarubicin	Idamycin	In combination with other approved antileukemic drugs for the treatment of acute	Pharmacia & Upjohn	F

		non-lymphocytic leukemia in adults.	Company	19
ifosfamide	IFEX	Third line chemotherapy of germ cell testicular cancer when used in combination with certain other approved antineoplastic agents.	Bristol-Myers Squibb	D 19
imatinib mesylate	Gleevec	Initial therapy of chronic myelogenous leukemia	Novartis	M 20
imatinib mesylate	Gleevec	metastatic or unresectable malignant gastrointestinal stromal tumors	Novartis	Fe 20
imatinib mesylate	Gleevec	Initial treatment of newly diagnosed Ph+ chronic myelogenous leukemia (CML).	Novartis	D 20
irinotecan	Camptosar	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company	Ju 19
irinotecan	Camptosar	For first line treatment n combination with 5-FU/leucovorin of metastatic carcinoma of the colon or rectum.	Pharmacia & Upjohn Company	A 20
irinotecan	Camptosar	Follow up of treatment of metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Pharmacia & Upjohn Company	O 19
letrozole	Femara	Treatment of advanced breast cancer in postmenopausal women.	Novartis	Ju 19
letrozole	Femara	First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.	Novartis	Ja 20
leucovorin	Wellcovorin, Leucovorin	Leucovorin calcium is indicated fro use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Immunex Corporation	Ju 19
leucovorin	Leucovorin	In combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.	Lederle Laboratories	De 19
levamisole	Ergamisol	Adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer.	Janssen Research Foundation	Ju 19
melphalan, L-PAM	Alkeran	Systemic administration for palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	GlaxoSmithKline	N 19
mesna	Mesnex	Prevention of ifosfamide-induced hemorrhagic cystitis	Asta Medica	De 19
methotrexate	Methotrexate	osteosarcoma	Lederle Laboratories	A 19
		For the use of UVADEX with the UVAR Photopheresis System in the palliative		

methoxsalen	Uvadex	treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.	Therakos	F 1
mitomycin C	Mitozytrex	therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.	Supergen	N 2
mitoxantrone	Novantrone	For use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.	Immunex Corporation	N 1
mitoxantrone	Novantrone	For use with other approved drugs in the initial therapy for acute nonlymphocytic leukemia (ANLL) in adults.	Lederle Laboratories	D 1
paclitaxel	Taxol	for use in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.	Bristol-Myers Squibb	Ju 1
paclitaxel	Taxol	Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	Bristol-Myers Squibb	A 1
paclitaxel	Taxol	Treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.	Bristol-Myers Squibb	D 1
paclitaxel	Taxol	First line ovarian cancer with 3 hour infusion.	Bristol-Myers Squibb	Ju 2
paclitaxel	Taxol	For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination therapy.	Bristol-Myers Squibb	O 1
paclitaxel	Taxol	New dosing regimen for patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary	Bristol-Myers Squibb	Ju 1
paclitaxel	Taxol	second line therapy for AIDS related Kaposi's sarcoma.	Bristol-Myers Squibb	A 1
paclitaxel	Taxol	For first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin.	Bristol-Myers Squibb	A 1
pamidronate	Aredia	Treatment of osteolytic bone metastases of breast cancer in conjunction with standard antineoplastic therapy.	Novartis	S 1
pegademase	Adagen (Pegademase	Enzyme replacement therapy for patients with severe combined immunodeficiency asa	Enzon	M

	Bovine)	result of adenosine deaminase deficiency.		199(
pentostatin	Nipent	Single agent treatment for adult patients with alpha interferon refractory hairy cell leukemia.	Parke-Davis Pharmaceutical Co.	Oct 1991
pentostatin	Nipent	Single-agent treatment for untreated hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms. (Supplement for front - line therapy.)	Parke-Davis Pharmaceutical Co.	Sep 199
plicamycin, mithramycin	Mithracin	Testicular cancer	Pfizer Labs	May 197(
porfimer sodium	Photofrin	For use in photodynamic therapy (PDT) for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with ND-YAG laser therapy.	QLT Phototherapeutics Inc.	Dec 199
porfimer sodium	Photofrin	For use in photodynamic therapy for treatment of microinvasive endobronchial nonsmall cell lung cancer in patients for whom surgery and radiotherapy are not indicated.	QLT Phototherapeutics Inc.	Jan (199
porfimer sodium	Photofrin	For use in photodynamic therapy (PDT) for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobroncial nonsmall cell lung cancer (NSCLC).	QLT Phototherapeutics Inc.	Dec 199
procarbazine	Matulane	lymphoma- Hodgkin's disease	Sigma Tau Pharms	Jul 2 196
streptozocin	Zanosar	Antineoplastic agent.	Pharmacia & Upjohn Company	May 1982
talc	Sclerosol	For the prevention of the recurrence of malignant pleural effusion in symptomatic patients.	Bryan	Dec 199
tamoxifen	Nolvadex	Breast cancer palliation	AstraZeneca Pharmaceuticals	Dec 197
tamoxifen	Nolvadex	to reduce the incidence of breast cancer in women at high risk for breast cancer	AstraZeneca Pharmaceuticals	Oct 199
tamoxifen	Nolvadex	Metastatic breast cancer in men.	AstraZeneca Pharmaceuticals	Apr 1993
tamoxifen	Nolvadex	In women with DCIS, following breast surgery and radiation, Nolvadex is indicated to reduce the risk of invasive breast cancer.	AstraZeneca Pharmaceuticals	Jun 200(
tamoxifen	Nolvadex	As a single agent to delay breast cancer recurrence following total mastectomy and axillary dissection in postmenopausal	AstraZeneca Pharmaceuticals	Dec 1986

		women with breast cancer (T1-3, N1, M0)		
tamoxifen	Nolvadex	For use in premenopausal women with metastatic breast cancer as an alternative to oophorectomy or ovarian irradiation	AstraZeneca Pharmaceuticals	Ma 19
tamoxifen	Nolvadex	Equal bioavailability of a 20 mg Nolvadex tablet taken once a day to a 10 mg Nolvadex tablet taken twice a day.	AstraZeneca Pharmaceuticals	Ma 19
tamoxifen	Nolvadex	For use in women with axillary node-negative breast cancer adjuvant therapy.	AstraZeneca Pharmaceuticals	Jun 19
tamoxifen	Nolvadex	to reduce the incidence of breast cancer in women at high risk for breast cancer	AstraZeneca Pharmaceuticals	Oct 19
temozolamide	Temodar	Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse with disease progression on a nitrosourea and procarbazine containing regimen	Schering	Au 19
teniposide, VM-26	Vumon	In combination with other approved anticancer agents for induction therapy in patients with refractory childhood acute lymphoblastic leukemia (all).	Bristol-Myers Squibb	Jul 19
thiotepa	Thioplex	Ovarian cancer	Immunex Corporation	Ma 19
topotecan	Hycamtin	Treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.	GlaxoSmithKline	Ma 19
topotecan	Hycamtin	Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the phase 3 study) or at least 90 days (in the phase 2 studies) after chemotherapy	GlaxoSmithKline	No 19
toremifene	Fareston	Treatment of advanced breast cancer in postmenopausal women.	Orion Corp.	Ma 19
tretinoin, ATRA	Vesanoid	Induction of remission in patients with acute promyelocytic leukemia (APL) who are refractory to or unable to tolerate anthracycline based cytotoxic chemotherapeutic regimens.	Roche	No 19
Uracil Mustard	Uracil Mustard Capsules	lymphoma-non-Hodgkin's	Roberts Labs	Sep 19
valrubicin	Valstar	For intravesical therapy of BCG-refractory carcinoma in situ (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.	Anthra --> Medeva	Sep 19

vinblastine	Velban	testicular carcinoma	Eli Lilly	No 19
vincristine	Oncovin	Wilms tumor	Eli Lilly	Jul 19
vincristine	Oncovin	acute lymphoblastic leukemia	Eli Lilly	Jul 19
vincristine	Oncovin	lymphoma-non-Hodgkin's	Eli Lilly	Jul 19
vincristine	Oncovin	lymphoma-Hodgkin's	Eli Lilly	Jul 19
vincristine	Oncovin	rhabdomyosarcoma	Eli Lilly	Jul 19
vincristine	Oncovin	soft tissue sarcoma	Eli Lilly	Jul 19
vincristine	Oncovin	neuroblastoma	Eli Lilly	Jul 19
vinorelbine	Navelbine	Single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC).	GlaxoSmithKline	De 19
zoledronate	Zometa	the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy	Novartis	Fe 20